A multi-dimensional approach for early identification of increased risk of falling in early-onset Parkinson`s disease patients

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von
Dipl.-Sportwiss. María Moreno Catalá

Präsident der Humboldt-Universität zu Berlin:
Prof. Dr. Jan-Hendrik Olbertz

Dekanin der Kultur-, Sozial- und Bildungswissenschaftlichen Fakultät:
Prof. Dr. Julia von Blumenthal

Gutachter:
1. Prof. Dr. Adamantios Arampatzis
2. Prof. Dr. Kirsten Legerlotz
3. Prof. Hendrik Schmidt

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Zusammenfassung

Die Parkinson Krankheit (PD) ist eine chronisch degenerative Erkrankung, bei der das neuromuskuläre Kontrollsystem aufgrund einer Degeneration der Dopaminneuronen in der Substantia Nigra (Basalganglien) fehlerhaft arbeitet. In der Gesamtbevölkerung sind etwa 0.3% betroffen, davon werden 10% vor dem 51. Lebensjahr diagnostiziert (früheinsetzende PD). Gleichgewichtsstörungen und Stürze gehören zu den wichtigsten Symptomen dieser Krankheit und betreffen mehr als zwei Drittel der PD-Patienten. Diese sind mit einem Verlust der Selbständigkeit und hohen Kosten für das Gesundheitsfürsorge-System verbunden. Trotz großer Fortschritte bei pharmakologischen und chirurgischen Behandlungen dauern Gang- und Gleichgewichtsdefizite noch an. Bei früheinsetzender PD werden diese Probleme durch Nebenwirkungen der Medikation, wie motorische Fluktuationen und Dyskinesien, zusätzlich verstärkt. Daher scheint die Entwicklung von bewegungsbasierten Therapien eine gute Alternative darzustellen, um die Sturzgefahr von jungen PD-Patienten zu verringern. Allerdings mangelt es derzeit an effektiven und spezifischen Interventionen aufgrund des noch sehr limitierten Verständnisses der zugrunde liegenden Mechanismen, die zum erhöhten Sturzrisiko bei früheinsetzender PD beitragen. Die vorliegende Arbeit zielt darauf ab, solche Mechanismen zu identifizieren und eine effektive Methode zur Früherkennung des Sturzrisikos bei früheinsetzender PD zu entwickeln.

Wir untersuchten den Beitrag der wichtigsten Faktoren für das erhöhte Sturzrisiko - zentrale und periphere neuromuskuläre sowie sensomotorische Fähigkeiten, dynamische Stabilitätskontrolle und Anpassungsfähigkeit der Fortbewegung - auf die Sturzrate junger PD-Patienten mittels eines Vergleichs zwischen gesunden Probanden und Patienten mit früheinsetzender PD mit und ohne Sturzerfahrung (Fallers vs. Non-Fallers). Dafür wurden in drei experimentellen Studien die 3D kinematische Analyse, Dynamometrie und Twitch Interpolationstechnik verwendet. Der Vergleich zeigte, dass sich die Fallers von den Non-Fallers darin unterschieden, dass sie zentral begründete Defizite in der Muskelkraft ihrer Beinstrecker (ersichtlich durch erhöhte antagonistische Momente und Aktivierungsdefizit der Agonisten) aufwiesen sowie eine beeinträchtigte Fähigkeit den Mechanismus „Vergrößerung der Unterstützungsfläche“ als Antwort auf simulierte Vorwärtsstürze anzuwenden. Beides resultiert im Vergleich mit der Kontrollgruppe in einer verringerten Abfangleistung. Die Parameter „Muskelkraft“ und „Annäherung an die vordere Stabilitätsgrenze“ identifizieren gemeinsam in 90% der Fälle junge PD-Faller. Darüber hinaus zeigten PD-Patienten eine uneingeschränkte prädiktive Anpassungsfähigkeit auf Gangstörungen, aber ein weniger stabiles Gangmuster und weniger effektive reaktive Antworten auf unerwartete und wiederholte Gangstörungen im Vergleich zu gesunden Kontrollpersonen.

Zusammenfassend zeigen diese Ergebnisse, dass junge PD-Patienten mit einem erhöhten Sturzrisiko von einem Krafttraining der Beinstrecker und Training der dynamischen Stabilität profitieren können. Da deren prädiktive Anpassungsfähigkeit nicht eingeschränkt war, sollten Trainingsinterventionen vor allem auf das reaktive Bewegungsverhalten zielen. Diese Arbeit stellt relevante Informationen dar, die für die Entwicklung von alternativen nicht-medikamentösen Therapien zur Verbesserung der posturalen Stabilität und zur Reduzierung des Sturzrisikos bei früheinsetzender PD nützlich sein könnten. Darüber hinaus wurde eine akkurate Methode zur Früherkennung von jungen PD-Patienten mit einem erhöhen Sturzrisiko erarbeitet, welches in einer klinischen Umgebung effektiv eingesetzt werden kann.

Abstract

Parkinson`s disease (PD) is a chronic neurological disease, in which the neuromuscular control system becomes faulty, mainly because of the degeneration of dopaminergic neurons in the nigrostriatal systems (basal ganglia). It affects 0.3% of the total population, 10% of whom are diagnosed before the age of 51 (early-onset PD). Postural instability and falls are some of the main symptoms associated with this disease, affecting more than two-thirds of PD patients. Despite advances in pharmacological and surgical treatments, gait and balance deficits still persist and are associated with loss of independence and immobility as well as high costs for healthcare systems. In the case of early-onset patients, these problems are worsened by medication-related side-effects, such as motor fluctuations and dyskinesia. Exercise-based therapies could be a good alternative for reducing the risk of falling in young PD patients. However, there is a lack of effective task-specific training interventions due to our limited understanding of the underlying mechanisms contributing to falls in early-onset PD. The present thesis aims to identify those mechanisms responsible for falls and to develop a sensitive method of assessment for the purpose of early discrimination of patients at risk of falling in early-onset PD.

We investigated the contribution of the most relevant factors susceptible of being responsible for the increased risk of falling (e.g. central and peripheral neuromuscular and sensory-motor capacities, dynamic stability control and locomotor adaptability) in order to determine the incidence of falls in young PD patients by means of comparing healthy controls and early-onset PD fallers and non-fallers. A combination of 3D kinematic analysis, dynamometry and twitch interpolation technique was used to assess these factors in three experimental studies.

The comparison revealed that young PD fallers differ from PD non-fallers in that they show central originated deficits in leg extensors` muscle strength - evidenced by increased antagonistic moments and activation deficit of the agonists - and an impaired ability to apply the mechanism “increasing the base of support” in response to simulated forward falls, both resulting in decreased recovery performance, when compared to controls. The factors “muscle strength” and “approach to the anterior limit of stability” together were shown to correctly classify 90% of the young PD fallers. In addition, while young PD patients show unaltered predictive adaptability to gait perturbations, they exhibit less stable gait patterns (i.e. lower margin of stability during unperturbed walking) and less effective reactive responses to unexpected and repeated gait perturbations compared to healthy controls.

The results revealed that young patients with an increased risk of falls may benefit from leg-extensors' strengthening and dynamic stability training. Since their predictive adaptability was not found to be altered, exercise interventions should focus on the reactive behavior. This thesis provides relevant information for the development of alternative non-medication based therapies aiming to improve postural stability and reduce falls in early-onset PD patients. It also provides an accurate assessment tool for the early identification of young PD patients at a high risk of falling that could be easily implemented in a clinical environment.

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1. Introduction and literature review

The following literature review summarizes the fundamental aspects of recent research on postural stability and falls in Parkinson`s disease patients. Firstly the most relevant aspects of Parkinson`s disease itself are introduced, with regard to its epidemiology, neural degeneration processes, as well as symptoms and current treatment techniques. Secondly, the importance and impact of falls in this population are presented, giving particular attention to the lack of studies in young patients. Thirdly, the main fall risk factors are discussed and current experimental results related to Parkinson`s disease patients are analyzed. Finally, the main benefits of exercise on Parkinson-related neural degeneration are reviewed and the effects of exercise interventions used in experimental attempts to reduce the risk of falling in Parkinson patients are discussed.

1.1 Parkinson's disease

1.1.1 Epidemiology

Parkinson`s disease (PD) is a chronic progressive neurological disease resulting in a degeneration of dopaminergic neurons in the substantia nigra systems (basal ganglia) (Poirier and Sourkes, 1965; Rubinstein et al., 2002). It is the second most common Central Nervous System (CNS) disease, after Morbus Alzheimer (Guttmacher and Collins, 2003; Squire, 2012) and, along with other neurodegenerative diseases, is expected to surpass cancer as the second most common cause of death by the year 2040 (Bloem et al., 2004a).

It presently affects 0.3% of the total population and 1% of people over 65 years of age in industrialized countries (Fahn, 1987; Crizzle and Newhouse, 2006), although in the future it is expected to affect 33% of older adults (Lilienfeld and Perl, 1993; Hirsch et al., 2009). Epidemiological studies have shown an estimated worldwide incidence ranging from 16 to 19 per 100,000 people per year (Bloem et al., 2004a). According to the estimated increase in life expectancy, future demographic projections predict a larger population over the age of 60 years in the developing regions, with a corresponding increase in the number of Parkinson`s disease patients.

Both direct and indirect costs for the treatment of Parkinson`s disease patients, including the cost of drug treatment, can be substantial and also increases as the disease progresses (Kaltenboeck et al., 2012). Kowal et al. place the national economic burden of PD over $14.4 billion only within the USA (Kowal et al., 2013). A recent meta-analysis reported the average excess direct costs to be $303,754 per patient with a life expectancy of 12.8 more years post-diagnosis and 6.96 years of quality-adjusted life (Johnson et al., 2013).

Recent research on the economic burden of PD showed that a scenario in which PD symptoms progressed only 20% slower than the average case would result in net monetary benefits of $75,891 per patient. The net monetary benefit would come from a $37,927 decrease in direct medical costs, 0.45 increase in quality-adjusted life-years, and a $15,235 decrease in lost income (Johnson et al., 2013).

1.1.2 Neural pathophysiology

The basic phenomenon in the genesis of PD is a dopaminergic neuronal loss, resulting in a decrease in the amount of the available dopamine in the brain. Recent studies provide evidence that degeneration begins in the dorsal motor nucleus of the vagal nerve and olfactory nucleus (followed by the lower brain stem, the basal ganglia, forebrain and the cortex) (Braak et al., 2003; Braak and Del Tredici, 2008). However, the major responsible cause for the PD-related motor symptoms is still attributed to the loss of dopaminergic neurons from the substantia nigra. Studies have shown that Parkinson patients have a loss of more than 80% of their dopamine producing cells in the substantia nigra (Korman, 1993; Kandel et al., 2000). Nevertheless, some motor as well as non-motor symptoms respond poorly to dopaminergic medication and might be a result of degeneration of other parts of the brain (Fox et al., 2008; Allen, 2010).

The dopaminergic neurons control the function of the extrapyramidal system that processes the movement information from the cortex to the striatum and returns it via the thalamus back to the cortex (Rissanen, 2012). This circle provides a possibility for the brain to change the effectiveness of transmission (of the excitatory cortical projections) in the basal ganglia motor loop based on attentional and emotional factors (Latash, 2008). The loss of dopaminergic input from the substantia nigra pars compacta to the striatum leads to increased activity in the indirect pathway and decreased activity in the direct pathway (see Fig. 1.1) because of the different actions of dopamine on the two pathways. Both of these changes lead to increased activity in the internal pallidal segment (GPi), which results in increased inhibition of thalamocortical and midbrain tegmental neurons and thus the hypokinetic features of the disease. These abnormalities in the function of basal ganglia lead to the motor symptoms of PD (Wichmann and DeLong, 1996). Accordingly, akinesia and bradykinesia are no longer viewed as negative signs that reflect loss of basal ganglia function, but rather as positive signs that, like rigidity and tremor, result from

excessive and abnormal activity in intact structures (i.e. increased (excitatory) drive from the subthalamic nucleus to the internal pallidal segment) (Kandel et al., 2000).

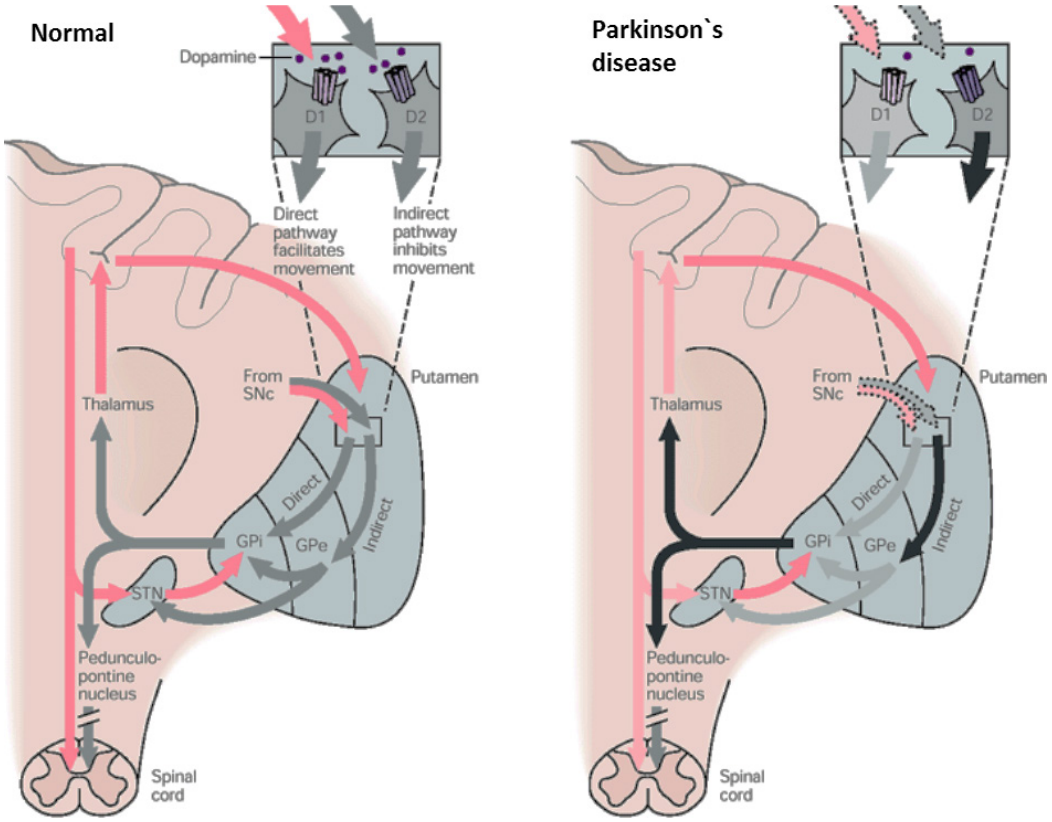

Fig. 1.1 The basal ganglia-thalamocortical circuitry under normal conditions and in Parkinson disease.
Inhibitory connections are shown as gray and black arrows; excitatory connections as pink and red. Degeneration of the nigrostriatal dopamine pathway in Parkinson disease leads to differential changes in activity in the two striatopallidal projections, indicated by changes in the darkness of the connecting arrows (*darker arrows* indicate increased neuronal activity and *lighter arrows*, decreased activity). Basal ganglia output to the thalamus is increased in Parkinson disease. *GPe* = external segment of the globus pallidus; *Gpi* = internal segment of the globus pallidus; *SNc* = substantia nigra pars compacta; *STN* = subthalamic nucleus. Adapted from Kandel et al., (2000). Principles of neural science, p. 861.

Acetylcholine plays a significant role in the stratium (Graybiel, 1990; Pisani et al., 2007) in the processing of motor and cognitive function, including muscle contraction, motor control, attention, memory and sleep-wake cycle regulation (Felder et al., 2000). Since the level of acetylcholine remains normal in PD, an imbalance in the number of dopamine vs. acetylcholine neurotransmitters is created. This imbalance interferes with some brain functions altering coordination and movement.

The reason why the number of dopamine producing nerve cells in the substantia nigra decreases is still unknown; however, some risk factors have been identified (Grosset, 2009). The majority of PD cases appear to be sporadic in nature; however, an estimated 10% of cases are familial, with

specific genetic defects (i.e. a-synuclein and parkin). Oxidative stress seems to play a prominent role in sporadic PD as well. Furthermore, other theories state that either an external or internal toxin (i.e. MPTP and neuroleptic drugs) selectively destroys dopamine creating neurons (Dawson, 2000; Squire, 2012).

1.1.3 Clinical diagnosis and symptoms

The diagnosis of PD is based on the presence of clinical symptoms and on the response to anti-parkinsonian medication (levodopa) (Hughes et al., 1992; Jankovic, 2008). It requires that two of the four primary symptoms (tremor, rigidity, bradykinesia and postural instability) are present (Gelb et al., 1999; Jankovic, 2008), normally bradykinesia and one of the other three (Hughes et al., 1992). The diagnostic accuracy is 75% according to clinicopathological studies, but can be as low as 70% in the early stages of the disease (Tolosa et al., 2006). A significant reason for the low diagnostic accuracy is due to the existence of other diseases with similar symptoms to PD (Tolosa et al., 2006), for example essential tremor (Grosset, 2009), multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration and Lewy body dementia (Pahwa and Lyons, 2010). Imaging techniques, such as the positron emission tomography (PET), single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI), can help to some extent in differentiating PD from other similar diseases (Tolosa et al., 2006). However, the imaging methods are costly and not all of them are widely available.

The rate of disease progression is individual and highly variable among PD patients (Grosset, 2009), but seems to be related to the symptoms at the onset of the disease. For example, patients with early prominent postural instability and gait disturbances (PIGD) at disease onset (Bohnen et al., 2011) tend to progress faster than patients with tremor-predominant disease at onset, which tend to be at a lower risk of experiencing falls (Hiorth et al., 2014).

There are four cardinal symptoms of PD: bradykinesia, tremor, rigidity and postural instability (Jankovic, 2008):

Bradykinesia usually refers to slowness of voluntary movement, but may also refer to deficits in spontaneous or automated movements (Jankovic, 2008; Latash, 2008). The term is often used synonymously with akinesia (lack of movement) and hypokinesia (reduced amplitude of movement) and can affect any part of the body and be more or less generalized (Latash, 2008). Bradykinesia seems to be primarily caused by failure of the basal ganglia to adequately support cortical mechanisms during the preparation and execution of movement, resulting in slowed development of muscle force (Berardelli et al., 2001). It has been estimated that 77–98% of PD patients suffer from bradykinesia (Gelb et al., 1999).

Tremor consists of involuntary, rhythmic and oscillatory movements of body parts, which affect 80–90% of PD patients (Grosset, 2009). It is characterized by a 5 to 6 Hz alternating activity of

antagonist muscles controlling a joint (Latash, 2008). The parkinsonian tremor occurs most commonly during a resting condition and is often alleviated during voluntary movement; however, it may appear also during postural, kinetic or intention conditions (Milanov, 2000).

Rigidity is a sustained involuntary increase in muscle tone and appears as an increased resistance to externally imposed joint movements (Latash, 2008; Grosset, 2009). This resistance is present in both extensor and flexor muscles even during slow velocity stretch (Maurer, 2003). It affects 89–99% of PD patients (Gelb et al., 1999).

Postural instability is developed by most PD patients at some stage, normally in the late stages of the disease, leading to impaired balance and frequent falls. These impairments tend to worsen with increased disease severity (Beckley et al., 1991; Bloem et al., 2004a) and ageing (Samii et al., 2004), the latter probably potentiated through the natural age-related balance degeneration. It is often tested clinically using the postural stability item of the Unified Parkinson's Disease Rating Scale (UPDRS), where the individual is rapidly pulled backwards at the shoulders. While reduced postural stability or balance is considered to be a motor impairment on its own, other problems including bradykinesia, rigidity, dyskinesia, shuffling gait, narrowed base of support, stooped posture and cognitive impairment can all compound the balance problem and impede task performance (Bloem et al., 2001a). The emergence of postural instability marks the onset of increased risk for severe disability in PD patients as these patients are more likely to fall, have poor mobility, difficulty performing daily activities and reduced quality of life (Bloem et al., 2001a; Franchignoni et al., 2005). Up to 40% of patients with postural instability have multiple falls, which may result in injury (i.e. hip and wrist fractures) (Jahn et al., 2008; Bohnen et al., 2011).

Other recognized motor signs and symptoms include gait and posture disturbances such as *freezing of gait, festination* (rapid shuffling steps and a forward-flexed posture when walking with the center of gravity falling forward over the stepping feet (Jankovic, 2008; Nutt et al., 2011) and *dyskinesia* (involuntary movements, similar to tics or chorea, which can lead to twisting and repetitive motions in the limbs and difficulty performing voluntary movements; a common side effect of the dopamine replacement medication (Fabbrini et al., 2007)) and *dystonia* (involuntary muscle contractions characterized by muscle cramps), as well as speech, swallowing disturbances, voice disorders (Russell et al., 2010), mask-like face expression and small handwriting (Jankovic, 2008).

Freezing of gait is not one of the cardinal symptoms, but it is considered to be a classic feature of Parkinson`s disease (Jankovic, 2008). It has been defined as "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (Bloem et al., 2004a; Giladi and Nieuwboer, 2008). This symptom includes a wide range of movement impairments from patients not being able to initiate gait to episodes of shuffling forward with very small steps (no more than a couple of centimeters in length) (Nutt et al., 2011). It has been associated with disease severity and longer levodopa treatment (Macht et al., 2007).

The non-motor symptoms of PD include: dementia, depression, psychotic features (e.g. hallucinations), autonomic dysfunction, oculomotor abnormalities (Gelb et al., 1999), sensory abnormalities and cognitive deterioration (Snyder and Adler, 2007; Jankovic, 2008). Cognitive impairment affects around 25% of the newly diagnosed Parkinson's disease patients, leading to marked deteriorations in attention/executive function and memory (Muslimovic et al., 2005; Allen, 2010). In addition, 30% of these patients develop Parkinson's disease with dementia (Riedel et al., 2008).

1.1.4 Treatment: Pharmaceutical and surgical management

Although there is no cure for PD, some symptoms can be reasonably reduced with medication that aims either to increase the amount or to inhibit the breakdown of dopamine in the brain (Grosset, 2009; Gardian and Vecsei, 2010; Rissanen, 2012). Traditional therapies are based on dopamine replacement strategies and include levodopa (L-dopa) (Chen and Swope, 2007; Davie, 2008), which work to restore dopamine levels in the brain. Many motor symptoms (e.g. bradykinesia, tremor and rigidity) respond well to levodopa for the first five to seven years of treatment (Strecker and Schwarz, 2008; Botzel and Kraft, 2010). It is also common to use drugs that aim at prolonging the effects of levodopa (i.e. dopamine antagonists) to delay the OFF periods (Schapira, 2007; Strecker and Schwarz, 2008). In this way, ON phases denote the time when the anti-parkinsonian medication is working well and movement is fluent with less presence of the motor symptoms. While OFF phases indicate that the effect of medication has decreased and the motor symptoms are present again.

However, the majority of postural control and gait impairments associated with falls become progressively resistant to dopaminergic medication or can be unresponsive from the start (Devos et al., 2010; Horak and Mancini, 2013; Hung and Schwarzschild, 2013). Even with the development of newer and more effective anti-parkinsonian drugs, the benefits of drug therapy usually begin to wane after some years, and the long-term use of levodopa often leads to troublesome side effects like motor response fluctuations (ON/OFF timing) and drug related dyskinesias (Kandel et al., 2000; Grosset, 2009). A study from Johnson et al. suggests that changes in medical management of PD over the last two to three decades have not translated into changes in long-term disease progression (Johnson et al., 2013). This evidence highlights the need to explore non-dopaminergic approaches in order to treat balance and gait problems in PD (Bohnen et al., 2011).

In the last years, deep brain stimulation surgery (DBS) of the subthalamic nucleus (STN) or the globus pallidus internus (GPi) has been often used to manage symptoms in PD patients with more advanced disease (Schapira, 2007; Botzel and Kraft, 2010). Deep brain stimulation is a procedure in which a stimulating electrode is implanted within an identified target in the brain. When the stimulation is turned on, electrical signals are delivered to the brain to stimulate targeted areas that

control movement by interfering with and blocking the abnormal nerve signals that cause some of the PD symptoms. DBS is an effective treatment to reduce the symptoms that respond well to levodopa (bradykinesia, tremor and rigidity) (Schapira, 2007), as well as to improve motor fluctuations by reducing OFF time and dyskinesias (Clarke et al., 2009). It also allows for a reduction in the anti-parkinsonian medication dosage (Benabid et al., 2009). However, motor impairments that respond poorly to levodopa unfortunately tend to respond poorly to deep brain stimulation, e.g., postural instability and freezing of gait during ON phases (Schapira, 2007; Ferraye et al., 2008; Allen, 2010). In this way, the overall effects of DBS on gait and balance remain controversial. Bakker et al. published a literature review showing overall gait and postural stability improvements after surgery (Bakker et al., 2004). On the other hand, a more recent study showed that the subjects who received DBS had more falls and gait disturbances in the first 3 to 6 months after receiving surgery than the subjects who only received medical therapy (Weaver et al., 2009). In the long term it has been shown that DBS increases the control of bradykinesia, tremor and rigidity but worsens gait function (Rodriguez-Oroz et al., 2005; Ostergaard and Aa Sunde, 2006) and posture (St George et al., 2010; Castrioto et al., 2011). DBS can be initially associated to positive effects in balance and gait in the "on" medication state, but within two years after surgery, these symptoms become worse than the preoperative "on" medication state (by the STN stimulation), or remain similar to the preoperative state (by the GPi stimulation) (St George et al., 2010).

In conclusion, drug and surgical therapies seem not to cure or shorten the duration of the disease (Rascol et al., 2003; Savitt et al., 2006). There is no therapy which can really improve all the motor symptoms of PD and especially not the most problematic ones, like gait impairments, postural instability and falls (as can be seen in Fig. 1.2) (Fasano et al., 2012).

A wide variety of problems in Parkinson's disease has been shown to respond to non-pharmacological treatments. These include motor skills, balance, posture, gait, mobility as well as difficulties with the activities involved with daily life (Morris et al., 2001; Lun et al., 2005). Effective non-pharmacological and non-surgical treatments may reduce the need for medication and improve quality of life. There has been a considerable increase in the last two decades in the research and clinical interest in using exercise as an alternative treatment aiming to improve the motor symptoms in PD (van der Kolk and King, 2013). Currently, there is a growing body of research that highlights the role of physical exercise as an essential part of managing the disease, with potential neuroprotective mechanisms (Hirsch and Farley, 2009; Conradsson et al., 2012), which may slow, stop or reverse the progression of the disease or promote neurorestoration through adaptation of compromised signaling pathways (Hirsch and Farley, 2009). New investigations suggest neurochemical and neuroplastic changes after exercise and document particular aspects of mobility improving after exercise. Regular exercise has been shown to delay the appearance of parkinsonian features in persons already diagnosed with PD (Tsai et al., 2002) and has the potential

to help both motor (gait, balance, strength) (Ashburn et al., 2007; Allen et al., 2010a; Smania et al., 2010; Brienesse and Emerson, 2013) and non-motor (depression, sleep disturbances, anxiety) (Speelman, 2011) aspects of Parkinson's disease as well as secondary complications of immobility (cardiovascular, osteoporosis) (Speelman et al., 2011; van der Kolk and King, 2013). However, several questions remain unanswered, particularly regarding the underlying mechanisms responsible for deficits in gait and postural stability which are susceptible to improvement from physical training, and which specific exercises should be applied in the different stages of the disease.

Fig. 1.2 Synoptic diagram of the different motor and non-motor effects of deep brain stimulation at various targets.
For each Parkinson's disease feature, a prominent effect of deep brain stimulation is shown by a long radial distance from the center of the polygon. Non-motor features are shown on the left side of the graph and motor features are on the right side. Stimulation of some targets (e.g., the STN, Zi, or GPi) influences various features, particularly bradykinesia and rigidity, tremor, fluctuations, dyskinesias and PIGD, although this last one in a much smaller extent as the other ones. By contrast, Vim stimulation selectively affects tremor. STN implants also have a moderate effect on mood and apathy and a mild effect on cognition, whereas PPN implants moderately influence PIGD, sleep, and cognition. *STN*=subthalamic nucleus. *Zi*=zona incerta. *GPi*=globus pallidus interna. PPN=pedunculopontine nucleus. Vim=ventralis intermedius nucleus. *PIGD*=postural instability gait difficulty. *ICD*=impulse control disorders. Adapted from Fasano et al. (2012). Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. Lancet Neurol., Vol. 11, p. 437.

1.1.5 Clinical rating scales

Standardized rating scales are commonly used to evaluate the motor impairment and the efficacy of treatment in PD. The most widely used clinical rating scales are the Unified Parkinson's disease rating scale (UPDRS) (Fahn, 1987) and the Hoehn and Yahr staging scale (H&Y) (Hoehn and Yahr, 1967).

The *UPDRS* covers four domains: mentation and mood (UPDRS I), activities pertaining to daily life (UPDRS II), motor function (UPDRS III) and complications related to therapy (UPDRS IV) (Goetz et al., 2007). It assesses a total of 42 items, the symptoms and problems are rated on a five-point scale (and sometimes on a two-point scale - present or not). The motor examination section of the UPDRS can be used for numerically scoring the severity of the most significant motor symptoms of PD. In this examination, tremor is tested during a resting condition, in a postural condition of the arms and during movement. The rigidity is assessed by passively moving the major joints and bradykinesia by observing patient's while walking, face and voice, and testing hand, arm and leg movements. Concerns have been raised about the current UPDRS scale, as many elements of PD impairment and disabilities seem to be underrepresented and its use to capture non-motor elements of PD can be confusing. Therefore, the Movement Disorder Society has sponsored a revision of the UPDRS (Goetz et al., 2007; Goetz et al., 2008). For more details see appendix.

The Hoehn and Yahr (H&Y) is a widely used clinical staging scale for PD (Hoehn and Yahr, 1967). It gives a more basic description of parkinsonian disability and impairments than UPDRS III, using a five-point scale to provide a rough estimate of disease severity (Goetz et al., 2004). Increasing parkinsonian motor impairment can be charted from unilateral (Stage 1) to bilateral disease (Stage 2) without balance difficulties, to the presence of postural instability (Stage 3), loss of physical independence (Stage 4), and being wheelchair-bound or bed-bound (Stage 5). Progression along the H&Y scale correlates with motor decline and deterioration in quality of life (Goetz et al., 2004). We decided to use this scale in our studies, as it is recommended in the Core Assessment Program for Surgical Interventional Therapies in PD (Defer et al., 1999). In addition, a meta-analysis of seven prospective studies reported that the H&Y stage was more accurate in predicting falling in PD patients than the UPDRS scale (with a sensitivity of 72% and specificity of 62%; and 54% and 69% respectively for the prediction of the first fall) (Pickering et al., 2007).

A recognized problem with the original H&Y is that stage II is very wide and covers a large proportion of patients. For this reason, a modified version that includes two additional stages (1.5 and 2.5) is commonly used (appendix).

1.1.6 Early-onset Parkinson`s disease

The mean age of onset in PD is around 65 years, although 5–10% of cases, classified as early-onset PD (EOPD) or young-onset PD, begin at an early age (Golbe, 1991). There is a lack of consensus about the maximal age for EOPD since it has varied from 40 (Gomez Arevalo et al., 1997; Schrag et al., 1998) to 55 years (Selikhova et al., 2009; Rana et al., 2012). However, most studies define EOPD as Parkinson's disease diagnosed between the ages of 21 and 51 years (Schrag et al., 2000; Schrag and Schott, 2006; Marder et al., 2010), therefore this is the definition that we used in our studies. The prevalence of EOPD among those living in Europe is estimated to be 6.2 - 12 per 100,000 (Schrag et al., 2000). There seem to be more familial cases in early-onset patients, although whether the cause of EOPD is only hereditary or also caused by environmental factors remains controversial (Ludin and Ludin, 1989; Wickremaratchi et al., 2009b). Age at onset is inversely correlated with the frequency of genetic mutations in familial (Lucking et al., 2000) and sporadic (Periquet et al., 2003) cases, with approximately 9–20% of EOPD patients having mutations in the parkin gene (Wickremaratchi et al., 2009b).

Problems faced by this group are different from those faced by older subjects because they face decades with the illness (Calne and Kumar, 2008). The disease strikes at a time in life which, for many, is the most productive, rewarding, and demanding (Willis et al., 2013), thus, having a greater impact on occupational, and social functioning. A survey of early and late-onset PD patients indicates that despite similar disease severity, early-onset patients have poorer quality of life and are much more likely to retire early (Schrag et al., 2003; Wickremaratchi et al., 2009a). Consequently, patients with early-onset PD are anticipated to have several neuropsychological features (e.g. depression or anxiety) (Schrag and Schott, 2006; Knipe et al., 2011).

The clinical findings, motor impairments and the course of the disease are very similar in both cases, early and late PD onset (Ludin and Ludin, 1989; Giovannini et al., 1991). However, available evidence suggests that PD patients with a younger age at onset have a lower rate of dementia, a slower long-term disease progression, an increased rate of dystonia at onset and during treatment and an increased rate of motor fluctuations and early dyskinesia in response to levodopa treatment (Wickremaratchi et al., 2009a).

Cognitive impairments and psychotic side effects to medication are less frequent in EOPD (Giovannini et al., 1991; Wickremaratchi et al., 2009a). Numerous studies suggest that late-onset PD (LOPD) patients are at a higher risk of dementia (Hietanen and Teravainen, 1988; Ebmeier et al., 1990; Biggins et al., 1992), and that the incidence of dementia in EOPD aged under 65 years is negligible (Quinn et al., 1987; Dubois et al., 1990; Mayeux et al., 1992), yet these differences are thought to be due to the age difference rather than to the existence of different disease entities (Ludin and Ludin, 1989).

Conflicting views have been reported on the progression of the disease in EOPD since results are highly dependent on the method of measurement and the cut-off age used to define EOPD. In a

study of 60 EOPD (under 40 years) and 60 LOPD patients estimating disease progression as the interval from first symptom onset to the development of a bilateral clinical picture, 60% of the EOPD group developed bilateral involvement within 12 months of onset compared with 5% of the LOPD group (Giovannini et al., 1991). A more rapid establishment of the full-blown parkinsonian clinical picture was reported in terms of efficacy of medication and appearance of symptoms, which was also observed by Gibb, et al. and Quinn et al. (Quinn et al., 1987; Gibb and Lees, 1988). This may reflect earlier bilateral involvement in EOPD, but the relatively short follow-up period in these studies makes it difficult to generalize this finding. However, the majority of recent studies including two systematic reviews reveal that most patients with EOPD experience a slower progression of PD than LOPD patients in terms of motor features and preservation of cognitive function (Diamond et al., 1989; Lee et al., 1994; Wickremaratchi et al., 2009a). Several studies have concluded that age at onset was the best predictor of deterioration in PD over 5 to 6 years (younger onset (before age 50), slower progression) (Diamond et al., 1989; Hely et al., 1995). In the DATATOP study (with 800 patients), a retrospective estimate of progression showed more rapid progression in LOPD (onset above age 70) than EOPD (onset before age 40) (Jankovic et al., 1990). Indeed, EOPD patients matched for the H&Y stage with LOPD (onset above age 55) patients have been shown to have significantly longer duration of the disease (11.1 ± 6.8 and 7.1 ± 4.4 years, respectively) (Spica et al., 2013). A recent prospective study reported that this faster progression in LOPD (onset above age 59) was only appreciable in later evaluations (7th and 10th year after onset), while short term evaluation (by means of UPDRS scores) showed no significant differences between early and late-onset PD patients (Garcia-Ruiz and Luquin, 2012).

The frequent presence of dystonia at onset is presumably an alternative manifestation of dopamine deficiency in EOPD (Wickremaratchi et al., 2009a) and occurs with a frequency of between 14% and 57% of all cases (Quinn et al., 1987; Gomez Arevalo et al., 1997). Painful off-period dystonia, particularly affecting feet and ankles, is also more common in patients with EOPD occurring at a rate of 21–59% during treatment (Giovannini et al., 1991; Mehanna et al., 2014) and decreasing with advancing age at onset (around 5.6% in LOPD) (Mehanna et al., 2014).

Dyskinesia as an early complication of levodopa therapy is appreciably more common in EOPD (Giovannini et al., 1991; Wickremaratchi et al., 2009a). It has been reported to develop in 19-40% of EOPD patients (Schrag et al., 2000; Mehanna et al., 2014) and to decrease with advancing age at onset at rates of 70% vs. 13% (Mehanna et al., 2014), 40% vs. 15.6%; (Ku and Glass, 2010) and 80% vs. 20% (Kumar et al., 2005) for early and late onset, respectively. Levodopa-dose-related motor fluctuations (i.e. oscillations in the control of motor symptoms) also appear earlier and more frequently in EOPD than in LOPD (Golbe, 1991; Tsai et al., 2013).

Other motor symptoms like rigidity and painful cramps have been shown to be more frequent in EOPD (21.7%) compared to LOPD (8.2%) as the predominant initial symptoms (Mehanna et al., 2014). Regarding tremor, there is no consensus on its frequency in EOPD, having been reported

less, more and equally frequent as in LOPD (Gibb and Lees, 1988; Giovannini et al., 1991; Kostic, 2009). A recent retrospective review of more than 700 patients found no significant differences in the frequency of tremor or bradykinesia as the predominant initial symptom among age groups (Mehanna et al., 2014).

With regard to postural instability, EOPD patients have shown a greater delay to the onset of imbalance and falls (Hely et al., 1995; Selikhova et al., 2009; Ebersbach et al., 2013) and less probability to have gait disturbance as an early symptom (Gibb and Lees, 1988; Kostic, 2009), suggesting that this may reflect the confounding effects of age and co-morbidity. Nevertheless, falls are already common and disabling in EOPD and in relatively early stages of the disease (Bloem et al., 2001a; Voss et al., 2012), which then also has a high impact on quality of life in EOPD patients.

Although the treatment for early-onset is the same as for late-onset PD, younger patients may not be able to use certain medication at first. Due to the fact that EOPD patients face many years of gradual progression of disease and disability, there is a greater probability of developing various adverse effects of treatment as well as a decrease in quality of life (Kostic, 2009). With respect to surgical treatments, although EOPD patients have shown better improvement from subthalamic nucleus DBS (STN-DBS) in comparison with LOPD patients, higher prevalence of axial and non-levodopa-responsive symptoms seems to be inevitable in EOPD patients after STN-DBS (Merola et al., 2011; Baba et al., 2012). Despite the long-term improvements in the activities of daily life (partly through significant reduction of dopaminergic medication) after STN-DBS, young patients seem to have more transient stimulation dyskinesia (47.1%) and dopamine dysregulation syndrome (11.8%) after surgery, compared to LOPD (Tsai et al., 2013).

In Summary, the reviewed literature suggests that motor symptoms may be more notable at the beginning of the disease in EOPD, compared to LOPD, but the long term evolution of the disease seems to be slower in young patients. The higher frequency of motor fluctuations, dystonia and dyskinesia reported in EOPD are very incapacitating factors which reduce patients` mobility and level of activity. The combination of a more rapid deterioration of the therapeutic efficacy of levodopa and the earlier appearance of very disabling motor side effects have an especially high impact on functional performance; this illustrates how crucially important it is to develop alternative, non-pharmacological therapies aiming to reduce motor deficits and falls in these young patients.

1.2 Falls in Parkinson's disease

1.2.1 Prevalence of falls in Parkinson's disease

Postural instability and falls are among the most incapacitating features of Parkinson's disease (Bloem et al., 2001a). The rate of falling of elderly patients with PD is five times higher than the one of healthy subjects at a similar age (Koller et al., 1989; Bloem et al., 2001a). Several studies have analyzed the rate of falling in Parkinson patients; they reported that 50-68% of patients fell at least once in the previous year (Bloem et al., 2001a; Wood et al., 2002), and up to 35-50% of them suffered recurrent or injurious falls (Ashburn et al., 2001b; Bloem et al., 2001a; Wood et al., 2002). Accordingly, a similar fall rate was reported over a three-month period in a meta-analysis of six prospective studies (46%) (Pickering et al., 2007). It has been shown that PD patients do indeed have an increased risk of recurrent falls, which is nine times greater than the one in similarly aged healthy individuals (Bloem et al., 2001a; Hong et al., 2009). The rate of falls per recurrent faller has been found to be very high, ranging from 4.7 (Camicioli and Majumdar, 2010) to 67.6 (Nilsson et al., 2011) falls per year (average 20.8) (Allen et al., 2012). 70% of the falls reported by PD patients seem to be 'intrinsic' (due to patient-related factors), while in controls they are on average 'extrinsic' (due to environmental factors) (Bloem et al., 2001a). A recent study assessing 180 community dwelling PD patients aged 22-83 showed that falls more frequently take place outside (57.2%) and in the morning (53.9%), with as much as 38.9% of them being injurious falls (Gazibara et al., 2014). Nearly half of the PD-related falls occur during dynamic tasks, such as walking, turning, standing up or bending down (Morris et al., 2000; Bloem et al., 2001a; Ashburn et al., 2008). However, very little is known about the mechanisms underlying the locomotor disability in this population when walking in environments representative of real-world dynamic settings (Cole et al., 2011).

A close relationship between disease severity and falls (Jankovic, 2008) has been questioned because falls become increasingly prevalent in the middle stages of PD (Hoehn & Yahr stage 3–4). After stage 4 patients significantly reduce their motor activities and even become immobilized around stage 5 (Giladi et al., 1997), therefore, falls rarely occur in these stages (Ebersbach et al., 2013). With respect to the duration of the disease, some studies have shown a rather linear increase in the cumulative prevalence of fallers (Hely et al., 2005; Latt et al., 2009a) (Fig. 1.3). A younger age at the onset of PD and high responsivity to dopaminergic medication is associated with a longer latency of the occurrence of falls (Kempster et al., 2007; Ebersbach et al., 2013).

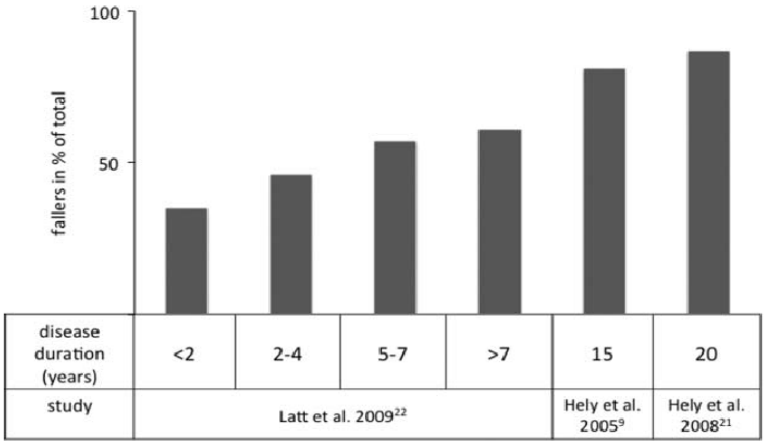

Fig. 1.3 Percentage of fallers in relation to disease duration in patients with PD.
(Ebersbach et al., 2013, Clinical Syndromes: Parkisonian gait. Mov. Dis., Vol.28, No. 11, p.1554).

However, although the occurrence of falls increases with disease severity (until H&Y stage 4) and ageing, some studies have reported that falls are already common and disabling in a relatively early stage of PD (Bloem et al., 2001a; Voss et al., 2012). A study with 413 PD patients with a disease duration lower than 5 years showed that a total of 23% of the participants already fell, and 11% were habitual fallers at this early stage of the disease (Voss et al., 2012). Fall frequency increased steadily with a rise in age and habitual fallers accounted for a larger proportion of fallers as age increased (Fig. 1.4). Although the fall frequency was lower in the younger age groups, 13% of individuals under age 50 and 18% of individuals between 50 and 64 years old fell during 12-18 months of follow-up (Voss et al., 2012).

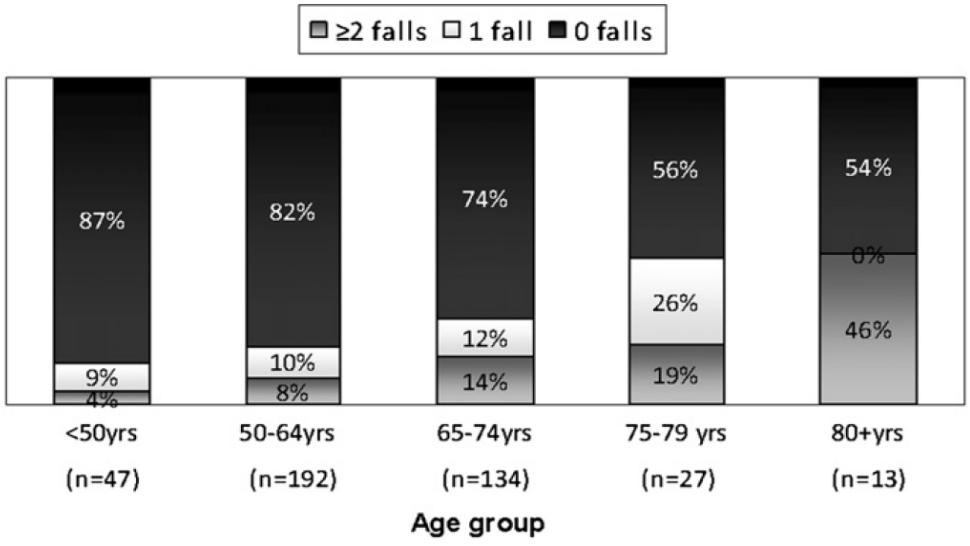

Fig. 1.4 Proportion and frequency of falls by age group.
"Falls" was defined by a score of greater than 0 on the UPDRS Falling at any visit or a report of the WHO term "Fall" on the adverse event log at any point in time during the

> course of the study. (Voss et al., 2012, Fall frequency and risk assessment in early Parkinson's disease. Parkinsonism and Related Disorders, Vol. 18, p. 838).

Furthermore, it is estimated that until 2030 the prevalence of Parkinson`s disease in developed countries will almost double (Dorsey et al., 2007); and consequently also the incidence of PD-related falls, having an even bigger impact on health care systems around the world.

Unfortunately there is very little research assessing the prevalence of falls in young or early-onset PD patients. The analysis of falls in young patients would provide a better understanding of the underlying mechanisms related to PD-related falls independent of the age-related balance degeneration.

1.2.2 The impact of falls in Parkinson's disease

The consequences of falls in PD patients are very significant, affecting not only the patients but also their families and the surrounding responsible health care system. Falls frequently result in injury, causing pain and short or long term disability and requiring costly medical treatment. Falls also contribute to an increase in the fear of falling, which consequently affects patients` daily lives, reducing their activity level and quality of life (Allen, 2010).

Almost half of the falls in PD result in injury (i.e. around 40%) (Bloem et al., 2004a; Gazibara et al., 2014). Although most of these injuries are soft tissue damage, more severe consequences like fractures also occur very frequently (Johnell et al., 1992; Pressley et al., 2003; Genever et al., 2005), in some of the reports reaching up to 56% of the cases (Cheng et al., 2014). The relative risk of fracture in PD patients is two times higher than in healthy individuals of the same age, especially for hip fractures (Johnell et al., 1992; Benzinger et al., 2014). It is estimated that upwards of 27% of PD patients will sustain a hip fracture in the first 10 years after being diagnosed with PD (Johnell et al., 1992). Hip fracture injuries resulting from falls in people with PD are therefore of particular concern leading to increased hospitalization, long-term care costs and reduced life expectancy (Dibble et al., 2008). The increase in severe injurious falls may be related to the reduced stepping capacity or recovery capacity associated with the disease (Jacobs et al., 2009; Allen, 2010), which increases the likelihood of landing on the floor after tripping. Similarly, there is also a correlation with abnormally directed arm movements in response to loss of balance. PD patients have been reported to adduct their arms against their body instead of using them to reach some support surface or to avoid the fall (Carpenter et al., 2004; Grimbergen et al., 2004). In summary, the reported fall-related injuries have a significant negative impact upon independent living and quality of life in PD patients (Morris, 2000; Cole et al., 2011).

The financial cost of falls for the health care system among PD patients is high. Falls and related injuries often lead to hospital admission. A study of more than 700 hospitalizations for PD patients showed that only 15% of them were related to primary management of the disease, while 13% of

them were related to falls (Temlett and Thompson, 2006). Furthermore, the costs related to treating fractures in PD are double or even triple than those seen amongst the healthy elderly (Pressley et al., 2003), which already averages over $30,000 per patient (Gehlbach et al., 2007). Another direct consequence of falls is an increased fear of falling. Some reports indicate that PD patients have a greater fear of falling than other individuals at a high risk of falling (Bloem et al., 2001a; Adkin et al., 2003). Fear of falling reduces patients` daily activity and quality of life. In this way, it has been highly associated to restrictions in the physical activity level (Bloem et al., 2004a) and in PD-specific quality of life measures like the PDQ-39 questionnaire ($R^2 = 0.74$) (Franchignoni et al., 2005).

Despite advances in anti-parkinsonian treatments, postural instability and falls do not seem to be prevented by pharmacological (Hall et al., 2013; Hung and Schwarzschild, 2013) or surgical techniques (Botzel and Kraft, 2010; St George et al., 2010). Therefore, the development of non-surgical and non-medication based therapies should be a priority for the decrease in the risk of falling in PD patients.

1.2.3 Why should we investigate postural instability in young PD patients?

Postural stability in PD patients tends to worsen with increased ageing (Samii et al., 2004; Hiorth et al., 2014). It worsens also with increased disease severity, which is normally coupled with ageing (Beckley et al., 1991; Bloem et al., 2004a). Even patients who report no falls at the beginning develop a change in the fall status after a few years of living with the disease. Hiorth et al. found an increase of more than 30% in the prevalence of falls in PD patients in a prospective follow-up period of 8 years, and identified ageing or higher age at baseline as the only risk factor related to recurrent falling (Hiorth et al., 2014).

In conclusion, a considerable number of studies report a strong association between ageing and falls in PD, probably as a result of the natural age-related balance degeneration. Since the mean age of disease onset is around 65 years, the majority of the studies are carried out with elderly PD patients. Most balance and gait behaviors currently associated with PD, such as slowed and variable gait and increased body sway, are not specific to this disease but to ageing (Horak and Mancini, 2013). Consequently it is very difficult to differentiate between the factors intrinsic to the disease and the factors resulting from the natural age-related degeneration. New findings regarding elderly PD patients is not directly transferable to young patients, since it is well known that the ability to control stability deteriorates also in healthy ageing (Wojcik et al., 1999; Pijnappels et al., 2005a; Karamanidis and Arampatzis, 2007).

Identifying the specific factors that relate to the underlying disease process in young PD patients, without the influence of the natural age-related balance degeneration, would contribute to

developing more effective training interventions aiming to reduce falls in young as well as in elderly PD patients. Although some studies have analyzed mixed groups of patients between 30 and 80 years of age (Allen et al., 2010b; Paul et al., 2014), none of those studies have been carried out in an entirely early-onset PD population, or entirely young PD sample. Consequently, there is a lack of studies analyzing the factor responsible for the reduced stability performance and the increased risk of falls in young-onset (< 51 years old) faller and non-faller PD patients.

On the other hand, to prescribe effective targeted interventions, one first needs to identify those patients at risk of falling within the general population (Bloem et al., 2001a; Bruijn et al., 2013) before one is able to establish the main determinants of fall risk in the individuals in question. It is, therefore, necessary to develop more effective assessing methods that may allow an early discrimination of individuals at risk of falling at a young age and in the early stages of the disease.

Since so little research has been made in young PD patients, all references used in this literature review regarding experimental research with PD patients refer to elderly or mixed participant groups - usually with a mean age older than 65 years - unless stated otherwise.

1.3 Risk factors for falls

Risk factors for falls in healthy elderly include impaired gait, lower limbs weakness, reduced balance, peripheral sensory deficits and visual, hearing and cognitive impairments (Tinetti et al., 1988; Bueno-Cavanillas et al., 2000; Shaw, 2002; Lord et al., 2003). As Parkinson`s disease mostly affects older people (mean age of onset above 65 years), these risk factors for falls are also present in the majority of the studies conducted with PD patients.

There have been some efforts to identify the specific risk factors for falls in PD in the last years (Ashburn et al., 2001b; Bloem et al., 2001a; Latt et al., 2009a; Kerr et al., 2010). Several studies, including a meta-analysis, have reported that the strongest predictor of falls is a previous history of falls (Ashburn et al., 2001b; Pickering et al., 2007; Latt et al., 2009a; Paul et al., 2013), which does not really allow for any primary prevention. The presence of the first fall event is not only relevant because of the disabling consequences of an injurious fall; it also triggers a set of sequential effects. The first fall increases the fear of falling, which results in the patient reducing their daily physical activity; consequently increasing degeneration of their balance ability and increasing their risk of future falls. This phenomenon highlights the importance of identifying the fall risk factors already in young PD patients (early disease onset: under 55 years (Marder et al., 2010)) and early stages of the disease in order to prevent falls in advance, before the first fall or injury occurs.

In this paragraph the present available information about the risk factor related to impaired motion and falls in PD will be presented and discussed.

1.3.1 Muscle strength

Intrinsic neuromuscular properties of the muscle-tendon unit have been shown to influence the function and performance of the entire musculoskeletal system during locomotion (Bassey et al., 1992; Karamanidis and Arampatzis, 2007). The capacity of the human system to generate rapid force for balance corrections after sudden perturbations during locomotion is especially affected by muscle strength and tendon stiffness (Karamanidis et al., 2008). The reduction of muscle strength with ageing is a well-known phenomenon (Schultz, 1995; Hughes et al., 2001; Karamanidis et al., 2008). It is accompanied by a reduction in contractile quality (Thelen et al., 1997; Manini and Clark, 2012) and in muscle mass, which can partly be explained by hormonal, immunologic and myocellular causes as well as by decreased muscular activity and a reduced protein intake with age (Vandervoort, 2002; Manini and Clark, 2012). As age advances, the size of the motor unit decreases as well as the number of excitable motor units and the maximal motor unit discharge frequency (Doherty et al., 1993; Klass et al., 2008). Reduced supraspinal drive and decreased spinal excitability with the ageing process (Manini & Clark 2012) may further contribute to diminished muscle performance. This decreased muscle strength, especially in the lower extremities, has often been related to the ability to prevent a fall after a gait perturbation (Pijnappels et al., 2008a; Pijnappels et al., 2008b) and has been shown to be an independent risk factor for falls in healthy elderly (Moreland et al., 2004).

However, in Parkinson patients, it is unclear whether or not the disease leads to muscle weakness, independently of the muscle strength reduction caused by ageing. Differences in muscle strength between elderly Parkinson patients (>65 years old) and healthy matched controls are reported by the majority of studies using maximal isometric contractions (Inkster et al., 2003; Paasuke et al., 2004; Oliveira et al., 2008). Studies of isokinetic strength have also consistently reported muscle weakness in Parkinson's disease compared to healthy controls (Koller and Kase, 1986; Nallegowda et al., 2004). Isokinetic strength testing involves movement at a constant predetermined velocity, thus, it is likely to be influenced by bradykinesia (Yanagawa et al., 1990). However, recent studies reported that the reduction of maximal muscle strength in PD patients is the major determinant of reduced muscle power in Parkinson patients, while other factors like bradykinesia of the lower limbs have a minor contribution (Paul et al., 2012a). Elderly PD patients also show decreased rate of force development (Paasuke et al., 2002; Paasuke et al., 2004), impaired ability to maintain constant force (Kunesch et al., 1995) as well as increased muscle co-activation during balance perturbation tasks (Horak et al., 1996; Dimitrova et al., 2004).

The reported muscle weakness in elderly Parkinson patients has been related to performance deficits by several functional and clinical tests like the chair-rising test (Paasuke et al., 2002), the time up and go test (Kerr et al., 2010) and the retropulsion test (Bloem et al., 2001a). In the same way, it has been associated with walking speed (Nallegowda et al., 2004) and the center of pressure-center of mass moment arm during gait initiation (Nocera et al., 2010). Deficits in these functional tasks could potentially result in situations where the individual is at risk of falling and therefore explain the increased rate of falls in this population (Schilling et al., 2009). Recently, Latt et al. (2009) reported that muscle weakness in older PD patients was one of the four main independent risk factors for falls, and especially for indoor falls (Gazibara et al., 2014). They developed (Latt et al., 2009a) an explanatory model using muscle weakness as one of the factors, which correctly classified 77% of the fallers and 82% of the non-fallers in between the patients of their study (Latt et al., 2009a). This assumption has been supported by following studies which significantly associated reduced leg muscle strength and falls retrospectively (Ashburn et al., 2001b; Robinson et al., 2005; Latt et al., 2009a) and prospectively (Latt et al., 2009a; Paul et al., 2013).

These results give evidence that maximal muscle strength remains to be one of the most relevant parameters regarding mobility and postural stability in Parkinson patients. However, the disease-related decrease in muscle strength may result from both central (i.e. arising from the central nervous system) as well as peripheral factors (i.e. occurring distal to the neuromuscular junction) (Thijs et al., 1998; Gandevia, 2001). To date, the contribution of these factors to muscle weakness is still not well understood, especially in young Parkinson patients. While the contractile capacities of muscles in PD patients seem to be unaltered (Hufschmidt et al., 1991), there are some reports suggesting deficits in the central ability to produce and control muscle strength. In this way, Filion et al. suggested that the basal ganglia are important for filtering out somatosensory noise and producing proprioceptive-specific antagonist muscle activation (Filion et al., 1988). Functional imaging studies in human and nonhuman primates showed that tonic dopamine release by the basal ganglia is responsible for focusing the patterns of muscular activity used to reach a goal by filtering out unwanted muscle activation not integral to the movement (Kropotov and Etlinger, 1999; Filion, 2000). Accordingly, reports on elderly PD patients confirmed increased muscle co-activation during balance perturbation tasks, due to larger and earlier than normal antagonist activity as a result of excessive tonic background EMG (Dietz, 1993; Dimitrova et al., 2004). In addition, transcranial magnetic stimulation in parkinsonian patients has also shown decreased corticomotoneuronal activation in PD (Glendinning and Enoka, 1994). These experimental evidences suggest that decline in muscle strength among PD patients might be triggered by central changes secondary to PD (and not by normal ageing), including accelerated loss of striatal neural tissue and concomitant depletion of striatal dopaminergic metabolites (Hirsch, 2009).

However, the majority of the reported information about this topic comes from studies investigating non humans or elderly Parkinson patients (on average over 65 years old). In Chapter 3, the first study evidencing the contribution of central and peripheral factors on muscle weakness in young PD patients will be presented.

1.3.2 Dynamic stability control

Postural control is an essential requirement for locomotion and all voluntary movements (Patla, 2003; Shumway-Cook and Woollacott, 2007). Balance or postural stability is a "generic term to describe the dynamics of body posture to prevent falling" (Winter, 1995b). Balance requires maintenance of the vertical projection of the center of mass (CM) within the limits of the base of support (BS) (Shumway-Cook and Woollacott, 1995; Winter, 1995a). During static equilibrium, like sitting or standing, we are primarily concerned with the control of position of CM within BS. However, this condition is insufficient in dynamic situations (i.e. moving to a new base of support while walking or running) (Pai and Patton, 1997; Iqbal and Pai, 2000). During locomotion, stability is challenged because the BS and the CM are in motion, with the BS changing its size and moving at a different speed compared to the speed of CM (Patla, 2003). It is in these situations where Hof`s concept of dynamic stability comes into play. In order to maintain the control of dynamic stability during locomotion the velocity of the CM must also be accounted for, since even if the CM is above the BS, balance may be impossible if CM velocity is directed outward. The reverse is also possible: even if the CM is outside the BS, but its velocity is directed towards it, balance can be achieved (Hof et al., 2005). Postural adjustments to maintain dynamic stability depend on the task, the context and the intention of the subject (Horak, 2006; Shumway-Cook and Woollacott, 2007).

1.3.2.1 Predictive and reactive motor behavior

The mechanisms for the control of stability can be categorized into two groups: *proactive* and *reactive* mechanisms.

Predictive control of stability can be classified as a proactive strategy and relies on the estimation of expected perturbations generated by ongoing movements or other concurrent movements. It is based on past experience and relies on knowledge about the environment which was generated from earlier experiences or which is available prior to the execution of the intended movement. These mechanisms are utilized in predictable situations (Patla, 2003; Bierbaum et al., 2011).

The predictive control of movements is thought to be regulated by supraspinal structures (Morton and Bastian, 2006; Jayaram et al., 2011), mainly by the cerebellum (Bastian, 2006; Ramnani, 2006), involving cognitive processes like attention and working memory (Strick et al., 2009), which may not be damaged in early stages of the disease in young Parkinson patients. It is assumed

that the cerebellum is provided with a copy of the motor commands, the so-called efference copy, which is used as input to a forward model. The forward model uses the efference copies to predict the new state of the body after executing the motor commands and further to predict the sensory consequences (Ramnani, 2006; Bierbaum, 2013). Predictive responses are important components for safety locomotion because they can improve dynamic stability by counteracting an expected perturbation during the ongoing movement, thus reducing its consequences (Marigold and Patla, 2002; Pai et al., 2003) and decreasing the risk of falls.

Anticipatory control, as well as predictive control, is considered a proactive strategy. It is based on identification of potential perturbation based on sensory input, this primarily being visual input guided by past experience (Patla, 2003).

Reactive control relies on sensory detection of unexpected perturbations to dynamic stability (Patla, 2003). Reactive mechanisms are generated by the use of feedback information requiring input from all major sensory systems, vision, vestibular, and kinesthetic, and therefore, depend on knowledge which is received during the movement. These reactive mechanisms may be automatic (reflexes) or volitional (e.g. stepping response). They range from passive tissue properties that can provide a response instantaneously to voluntary response occurring around 200 ms and aim at the modification of movements which are already in progress (Patla, 2003). This modification may be necessary because of an incorrect feed-forward plan or the development of unpredictable perturbations (Tseng et al., 2009). Subcortical neural centers, such as spinal cord or brain stem, are thought to be responsible for the reactive adjustments (Morton and Bastian, 2006). Expectation, attention, intention and the environmental context, together with preprogrammed muscle activation patterns (synergies) influence the reactive responses (Horak et al., 1997; Bierbaum, 2013).

Reactive and predictive adjustments are separate components of postural control (Macpherson et al., 1989). It has been suggested that they may be modulated by distinct basal ganglia-cortical circuits (Hall et al., 2013).

1.3.2.2 Mechanisms and strategies for the control of dynamic stability

Postural mechanisms or strategies to control dynamic stability are based on behavioral goals (i.e. what the central nervous system attempts to control), specific tasks and the environmental context. They are characterized by their kinematic and kinetic patterns and the applied muscle synergies (Horak et al., 1997). These general conditions underlie biomechanical and neural constraints and generate the required muscle output according to the prioritization of control variables, such as control of the center of mass, head or trunk orientation (Horak et al., 1997; Bierbaum et al., 2013). During unexpected perturbations of the dynamic stability state the center of mass is suddenly accelerated, thus, compensatory reactions need to be applied to decelerate the center of mass (Maki and McIlroy, 2006). The motion of the center of mass can be slowed down by the generation of muscle torque at the ankle, knee, hip or other joints. Recovery strategies have been defined as

"ankle and hip strategies" (implying weight shifting at those joints) and "stepping strategy" or "change-in-support" (consisting on the realignment of the base of support). The second form of strategy may be necessary when larger perturbations are applied (Maki and McIlroy, 1997). From a biomechanical point of view, there are three mechanisms responsible for maintaining dynamic stability after perturbations: (a) increasing the base of support, (b) counter-rotating segments around the center of mass and (c) applying an external force (not the ground reaction force) (Hof, 2007). The ankle and hip strategy may be assigned to the mechanism "counter-rotating segments around the center of mass" and the stepping strategy to the mechanism "increasing the base of support".

With regard to perturbations during walking, the control of dynamic stability is both phase-dependent and perturbation-specific (Nashner, 1980; Winter et al., 1990), i.e. the timing of the perturbation influences the preferred selected strategy. Those strategies are able to adapt to specific situations and may be learned through experience in various environmental contexts (Horak and Nashner, 1986).

On the neuronal level, the latency of postural responses is longer than that of spinal stretch reflexes but significantly shorter than that of voluntary movements (Jacobs and Horak, 2007). Figure 1.5 shows a recent model of proposed neural pathways which are responsible for short, medium and long latency responses as a result of perturbations.

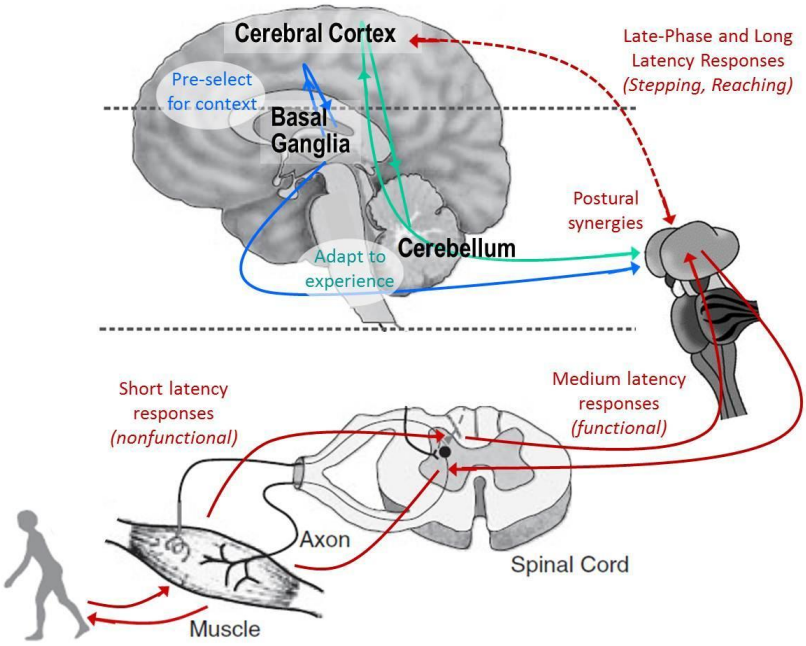

Fig. 1.5 Model of proposed neural pathways which are involved in the control of recovery responses.
The contribution of the short-latency activation is quite small, whereas whole body synergies, which include the medium and long latency responses, are functionally relevant. Short latency responses can be seen at about 40-50ms and long latency responses at about 120 ms after a

stimulus (Jacobs & Horak, 2007. Cortical control of postural responses. J Neural Transm., Vol. 114, p.1341).

The initial phase of the postural response seems to be controlled by the spinal cord and the brainstem. Late in the response there is evidence of transcortical reflex pathways, indicating participation of the cerebral cortex (Christensen et al., 2000; Taube et al., 2006). This may imply that compensatory reactions to control dynamic stability, like change-in-support responses, are characterized by an initial automatic phase and a late phase, in which a contribution of the cerebral cortex and thereby an influence of cognition may be possible (Norrie et al., 2002; Jacobs and Horak, 2007).

Furthermore, the control of static and dynamic stability relies on an accurate internal representation of stability limits. Those stability limits are related to the ability of an individual to execute certain recovery movements (Forner-Cordero, 2003). It is assumed that the human system controls the stability state in consideration of the motion state of the body center of mass (i.e. instantaneous position and velocity) with regard to the base of support (Pai et al., 2003; Hof, 2008). This means that the relationship between the motion of the center of mass and the base of support together with the underlying individual constraints determine the stability limits for each person. The internal CNS representation of stability limits as well as of the position and motion of the center of mass relative to the base of support has to be accurate to produce adequate control processes (Maki and McIlroy, 1999; Bierbaum et al., 2013).

1.3.2.3 Postural adjustment strategies in the regulation of perturbations in PD

Most of the regarding the effect of external perturbations in people with Parkinson's disease has analyzed responses to movements of the support surface on which participants are standing (Allen, 2010). Under these conditions PD patients generally show similar muscle activation latencies to that of neurologically healthy adults (Beckley et al., 1991; Dimitrova et al., 2004; Horak et al., 2005). As stated by Horak loss of balance is, therefore not due to a delayed response, but to an ineffective response (Horak et al., 1992). These responses are characterized by increased size of the destabilizing responses, inflexibility of response and excessive co-contraction of antagonist muscles (Allen, 2010). Excessive abnormal contraction of agonists and antagonist postural muscles in response to external perturbations seem to be a disease-related characteristic in people with Parkinson's disease (Horak et al., 1992; Horak et al., 1996; Dimitrova et al., 2004). Antagonist muscles tend to be activated too early and with excessive magnitude in the legs and trunk resulting in less effective postural muscle responses (Horak et al., 1996; Carpenter et al., 2004; Dimitrova et al., 2004). People with Parkinson's disease also show excessive background muscle activity (Horak et al., 1996; Dimitrova et al., 2004). This ineffective stiffening response results in directionally specific postural instability (Horak et al., 2005).

Increasing the base of support is also a common reaction after perturbations and crucial in preventing falls (Maki and McIlroy, 1997; Karamanidis et al., 2008). The compensatory steps made by people with Parkinson's disease have been found to be later, slower and shorter than neurologically-normal people of the same age (Jacobs and Horak, 2006; King and Horak, 2008). This may reduce the chances of the person with Parkinson's disease successfully recovering their balance and avoiding a fall. King and Horak (2008) suggested that some participants with Parkinson's disease had difficulty generating the lateral weight shift required to initiate successful compensatory stepping to a lateral platform perturbation. This study also provides evidence that people with Parkinson's disease can have difficulty selecting appropriate and consistent postural responses, resulting in a delayed or inadequate response, and consequently more falls (King and Horak, 2008).

Furthermore, laboratory studies have indicated that Parkinson`s disease also affects the ability to flexibly adapt postural response strategies when the perturbation characteristics or the initial conditions change (Horak et al., 1992; Chong et al., 2000), or when instructions change ("give in to" or "resist" the perturbation) (Bloem et al., 1995; Chong et al., 2000). For example, when postural perturbations change from a translation to a rotation or when support conditions change from maintaining stable support to no support, healthy individuals immediately modify their postural responses to take into account the new physical constraints of the situation. In contrast, patients with PD gradually adapt their responses, with trial and error, over several trials (Chong et al., 1999a). It seems, therefore, that people with Parkinson's disease are less able to modulate their postural responses to suit different body positions, tasks or environmental situations (Allen, 2010), highlighting the specific role of the basal ganglia in set-switching control mechanisms (i.e. in adapting postural response patterns for specific biomechanical conditions) (Horak and Mancini, 2013).

However, since most falls occur during dynamic situations (Tinetti et al., 1988; Rubenstein, 2006), the conclusions drawn from investigations on static postural control are not directly transferable to dynamic stability control (Owings et al., 2000; Mackey and Robinovitch, 2005). Imbalance and tripping over obstacles during gait have been reported as one of the most common causes of falls in older adults (Pavol et al., 2001). This is equally true in regards to PD, since tripping has been also identified as a common precursor to falls (Stack and Ashburn, 1999). Recent research on PD patients has reported a decrement in locomotor performance as well as disease-dependent decreases in velocity, step length (Galna et al., 2010; Stegemoller et al., 2012) and in the antero-posterior separation of foot and obstacle (Stegemoller et al., 2012) during obstacle crossing. Greater foot clearance over obstacles, as compared with age-matched healthy controls, has also been observed, suggesting that PD patients adopt a more conservative strategy during obstacle crossing (Stegemoller et al., 2012). This apparently conservative approach is coupled with an increased risk of obstacle contact (Chen et al., 1991&1994) and greater frontal plane motion during obstacle

crossing, which has been shown to be possible factors contributing to a greater risk of tripping in older adults (Chen et al., 1994; McFadyen and Prince, 2002). A moderate increase in medio-lateral center of mass range of motion while crossing obstacles has also been reported, which may result in a higher risk of falling sideways during obstacle crossing (Stegemoller et al., 2012; Galna et al., 2013). In addition, Oates et al. (2013) recently showed that PD affects walking speed and the ability to develop appropriate strategies to stop within one step and maintain stability during gait termination tasks on a slippery surface. They suggested that elderly PD patients have difficulties controlling their CM during this perturbed task (Oates et al., 2013). Furthermore, reports from Cole et al. also show that postural control deficits in elderly PD fallers may impair their capacity to attenuate changes on the walking surface when comparing walking on a hard floor to a foam surface (Cole et al., 2011).

1.3.3 Gait and freezing of gait

Walking becomes a task which cannot be performed
without considerable attention. The legs
are not raised to that height, or with that promptitude
which the will directs, so that the utmost
care is necessary to prevent frequent falls.
—James Parkinson, 1817

As described from James Parkinson almost two hundred years ago, gait disorders are one of the most identifying characteristics of Parkinson`s disease (Parkinson, 1817). They manifest in almost all cases of Parkinsonism, often leading to loss of mobility and increased mortality (Ebersbach et al., 2013).

Gait is a complex sensorimotor activity that involves spatial-temporal coordination of the legs, coordination of the trunk and arms, as well as dynamic equilibrium, all of which are affected by PD (Winter, 2009; Schoneburg et al., 2013). It has been demonstrated that individuals with PD have significantly slower gait with less foot clearance and smaller step lengths (Morris et al., 1994; Hausdorff, 2009). They also show increased time spent in the double support phase of gait as well as increased stride time variability (Hausdorff et al., 1998; Hausdorff, 2009). All these variables predict falling as they become more imminent (Schaafsma et al., 2003b; Brach et al., 2005; Hausdorff, 2007), probably due to the abnormal timing of central pattern generators or to an increase in compensatory foot placements to control poor balance (Horak and Mancini, 2013). Reduced trunk rotation (en-bloc) while walking and reduced arm swing are also specific early signs of gait impairments in PD (Zampieri et al., 2010). Also less rhythmic accelerations at the pelvis and head have been found in elderly PD patients suggesting that an inability to control displacements of

the torso when walking may predispose older people with PD to falls (Latt et al., 2009a). Supporting this suggestion, Cole et al. found that PD fallers had increased medio-lateral head motion compared with PD non-fallers and controls (Cole et al., 2010).

It has been shown that disturbances of gait represent one of the highest risk factors for falling in elderly PD patients (Hiorth et al., 2014). In a prospective long-term study, nearly 75% of PD patients reported falling after 8 years of follow-up, and disease-specific gait and axial impairments were the major risk factors for future falls in non-fallers at baseline (Hiorth et al., 2014). However, the majority of postural control and gait impairments associated with falls are resistant to dopaminergic treatment (Bohnen et al., 2006). While some gait parameters, including stride length, gait velocity, and movement amplitudes, improve with dopaminergic treatment (Bowes et al., 1990; O'Sullivan et al., 1998; Shan et al., 2001), other features, including temporal parameters (e.g. cadence, swing and stance duration), kinetic abnormalities, and gait variability are treatment resistant (Blin et al., 1991; O'Sullivan et al., 1998; Ebersbach et al., 1999). Furthermore, only few characteristics of gait are specific to PD (Hausdorff et al., 1997; Hausdorff, 2009). An examination of gait may lead to inconclusive results because slow and small stepped walking is often unspecific and can also be related to age, depression, or other conditions (Ebersbach et al., 2013). This highlights the importance of analyzing gait disorders in PD without the influence of these contaminating factors (e.g. ageing).

The Parkinson's disease related freezing of gait contributes notably to disability and falls in PD patients and correlates to disease progression. In the early stages of the disease the periods of freezing are usually short, causing only mild difficulty and rarely leading to falls (Schaafsma et al., 2003a; Bloem et al., 2004a; Allen, 2010). However, as the disease progresses, freezing occurs more often and for longer periods of time (Giladi et al., 2001), with the consequent restrictions in daily activities and walking ability (Morris et al., 2008). Furthermore, as freezing episodes are generally unpredictable, and as the Parkinson's disease is associated with impaired postural stability, freezing can cause such balance disturbances that result in falls (Bartels et al., 2003; Bloem et al., 2004a; Allen, 2010). Jacobs et al. suggested that when freezing is associated with a forward loss of balance, it may be due to an inability to link a normal postural adjustment to the motor pattern for stepping (Jacobs et al., 2009; Allen, 2010).

1.3.4 Adaptability and locomotor adaptability

Locomotor adaptation is a process during which changes in locomotor output are stabilized over time by the central nervous system's incorporation of feed-forward predictive motor actions and sensorimotor feedback (Morton and Bastian, 2006; Bares et al., 2007). Adaptations of gait pattern in response to internal and external environmental changes are essential for efficient and safe locomotion (Roemmich et al., 2014). Furthermore, the ability to retain adaptations in gait may be

important in the prevention of falling in healthy elderly (Pai et al., 2010). Therefore, with regard to fall incidence, it is important to investigate to what extent recovery strategies of PD patients can be adjusted after repeated exposure to perturbations.

1.3.4.1 Adaptability of PD patients

There is a growing body of research suggesting that storage and retention of learned upper extremity and visuomotor tasks are impaired in persons with PD (Smiley-Oyen et al., 2006; Bedard and Sanes, 2011; Leow et al., 2012). One recent study assessed the ability of PD patients to adapt hand movements to a visuomotor perturbation that is suddenly introduced - which produced large and consciously detected spatial errors - versus one that is introduced gradually over many trials - which exposed subjects to only small errors (Venkatakrishnan et al., 2011). PD patients worse adapted their movements to the sudden rather than the gradual perturbation, when compared to age-matched healthy subjects (Mongeon et al., 2013). This finding suggests that basal ganglia-related circuits are important neural structures for adaptation to sudden perturbations requiring awareness and high-cost action selection. Dopaminergic treatment may selectively compromise the ability to learn from large explicit movement errors for reasons that remain to be elucidated (Mongeon et al., 2013). Drawing on these results it would be logical to think that persons with PD may also exhibit restricted locomotor adaptation and diminished facilities for adaptive learning. However, it is still unclear whether these suggestions can also be applied to locomotor adaptive tasks, especially in early-onset patients.

Regarding locomotion, while persons with PD demonstrate difficulty altering the locomotor system during transitional periods such as turning (Bloem et al., 2001a), obstacle clearing (Stegemoller et al., 2012), and gait initiation (Hass et al., 2005), a certain ability to adapt to new walking conditions and to store new walking patterns has been reported to be present in PD (Oates et al., 2013; Roemmich et al., 2013). Nevertheless, this adaptability has been observed to be more limited in extent than in healthy controls (Oates et al., 2013) and has exhibited certain default asymmetry (e.g. in step or stride length), suggesting present but diminished locomotor adaptation ability in PD patients (Roemmich et al., 2013). These locomotor features may affect patients` capacity to adapt postural adjustments to perturbations during dynamic conditions and, therefore, increase their risk of falls. These results support existing evidence that the basal ganglia are involved in processing error information in the early phases of gain adaptation (Desmurget et al., 2003; Turner et al., 2003). L-dopa improves overall gross motor performance but can globally impair adaptation driven via visual feedback. For instance, Semrau et al. discovered that subjects in the PD OFF state, despite substantial motor impairments, demonstrated intact visuomotor adaptation to visual rotations. The results of this study suggest two important ideas: that PD patients have decreased early-phase gain adaptation driven via visual feedback and that L-dopa amplifies this impairment (Semrau et al., 2014).

Regarding the consolidation of adapted locomotor tasks, previous research in healthy adults has indicated that stride length adapts immediately in a rather drastic fashion upon exposure to a split-belt-treadmill walking task, then continues to adapt gradually throughout the task (Bruijn et al., 2012). Contrary to healthy controls, PD patients do not show any further alteration in stride or step length from early to late adaptation or to retention tests, suggesting that consolidation of the adapted motor task over time appears to be abnormal in PD (Marinelli et al., 2009; Roemmich et al., 2013).

However, when analyzing locomotor adaptability, it is important to consider the proactive as well as the reactive adaptation strategies. There has not yet been a study investigating the proactive and reactive modulation of locomotor adaptation in young PD patients. It is also important to consider that the examination of gait may lead to inconclusive results because of the non-specific features of gait disorders in PD. Challenging locomotor control with imposed environmental manipulations (i.e. external gait perturbations) can help to disclose more specific gait alterations in early stages of PD (Ebersbach et al., 2013). In chapter 5, the first results on predictive and reactive adaptability to gait perturbations in young PD patients will be presented.

1.3.4.2 Predictive adaptation with regard to perturbations of dynamic stability

Appropriate predictive or feed-forward control, based on prior experience and knowledge about the perturbation, may help to reduce the magnitude of the perturbation facilitating the reactive response and therefore counteracting the destabilizing effect of the perturbation (Bierbaum, 2013).

A few recent studies on dynamic stability in healthy older adults have suggested impairments in initial reaction to gait perturbations but preserved ability to predictively adapt to perturbations over time (Bierbaum et al., 2010; Pai et al., 2010). Very little research has been conducted on PD patients' predictive adaptation capacity; however, some results indicate similar ability to that of the healthy elderly. Roemmich, et al. (2014) reported that elderly PD patients exhibited a significant aftereffect in step length asymmetry after 10 minutes of split-belt-treadmill walking, showing clear predictive adaptation (Roemmich et al., 2014). The ability to retain this predictive adaptation was shown to be intact during a re-test after a wash out period of overground walking (Roemmich et al., 2014). Oates et al. (2013) found similar predictive strategies to diminish the destabilizing effect of stopping on a slippery surface between elderly PD patients and controls (Oates et al., 2013). In addition, Bares et al. (2010) found no significant differences between PD patients and controls in a predictive motor-timing task that involved mediated interception of a moving target, suggesting that the basal ganglia play a less significant role in predictive motor timing than the cerebellum (Bares et al., 2010). In any case, neither the predictive strategies in response to perturbed locomotion nor the adaptability of these responses has been investigated in young PD patients.

Predictive control and anticipatory control are both proactive strategies, although anticipatory control is not only guided by past experience but is also based on sensory input (Patla, 2003). The anticipatory postural adjustments (APAs) in PD have been investigated more thoroughly than the predictive adjustments. Parkinson`s disease-related APAs appear to be normal in terms of the general sequence of muscle activations (Aruin et al., 1996; Frank et al., 2000). However, abnormalities have been found in terms of the timing, speed and size of muscle activations (Frank et al., 2000; Bleuse et al., 2008).

Also self-initiated stepping tasks have shown small and slow postural adjustments (shorter steps) in Parkinson's disease patients (Jacobs et al., 2009; Mancini et al., 2009), which were present in both forwards (Burleigh-Jacobs et al., 1997; Mancini et al., 2009) and sideways directions (Tonolli et al., 2000). These small and slow adjustments have often delayed anticipatory unloading of the swing leg and therefore contribute to the reported reduced step length (Burleigh-Jacobs et al., 1997). In general, it seems that bradykinesia influences the size and speed of postural adjustments in preparation for voluntary movement (Allen, 2010). The ability to accurately rescale APAs while perturbed walking has also proven to be impaired in PD patients, affecting their ability to control dynamic stability and increasing their risk of falls. Studies on elderly PD patients reported that the refinement of APAs with task experience is compromised by anti-parkinsonian medication (Rocchi et al., 2006; Hall et al., 2013). Research on postural control during changes in perturbation condition showed that while controls immediately modify their anticipatory responses to take into account the new physical constraints of the situation, PD patients do not, resulting in a longer period of time needed for adaptation (Chong et al., 1999b; Horak and Mancini, 2013).

1.3.4.3 Reactive adaptation with regard to perturbations of dynamic stability

While research has shown that initial reactive adaptation to gait perturbations in healthy elderly is decreased compared to young adults (Bierbaum et al., 2010; Pai et al., 2010), the available studies regarding reactive adaptation in PD patients present controversial results. Roemmich et al. reported that PD patients and controls could adapt similarly during the first five strides of exposure to their split-belt treadmill (SBT) walking condition, suggesting that the spinal mechanisms governing reactive locomotor adaptation remain intact and effective in PD (Roemmich et al., 2014). This finding is consistent with previous research demonstrating that persons with PD were able to adapt to SBT walking similarly to healthy elderly over a short time period (Dietz et al., 1995). Furthermore, further literature exhibits that persons with PD are able to make mild alterations to gait during treadmill walking (Hong et al., 2007; Bello et al., 2008). However, while the reactive adaptation in the first study was defined as the mean stride length asymmetry over the first five trials - and in the second study over the last 20 trials - of exposure to SBT (Dietz et al., 1995; Roemmich et al., 2014), these responses cannot be considered purely reactive. Purely reactive

responses in consequence to perturbations are seen only in the first exposure to a perturbation. Following experiences with the same perturbation are characterized by modified timing, magnitude and coordination (Marigold and Patla, 2002; Patla, 2003). Participants base their motor response to split-belt condition on their first experience with the split-belt, and therefore adopt also predictive adjustments to the gait pattern. Walking speed is another limitation of these findings, since PD patients walked at a lower speed than controls. This different speed may have perturbed the stability state of the participants in different magnitudes, making it not possible to compare the demand produced by the split-belt condition between PD patients and controls. Dietz et al. also recognize that the healthy controls participating in their study could tolerate bigger differences in belt speed than the PD patients (Dietz et al., 1995).

On the other hand, other experimental reports have observed that elderly PD patients have impaired ability to adapt reactive postural adjustments to external perturbations (Schieppati and Nardone, 1991; Horak et al., 1992; Horak et al., 1996), as well as diminished ability to optimize postural response to changes in postural demand (Dimitrova et al., 2004; Horak et al., 2005). Nanhoe-Mahabier and colleagues showed less effective reactive responses to a first unexpected perturbation of the stand position (toe-up rotation of the support-surface) in elderly PD patients. However, after consecutive repetition of the perturbation, they could adapt their response. Even though the adaptation process was slower than in controls, PD patients still seemed to have the ability to adapt to perturbations (Nanhoe-Mahabier et al., 2012). In the same way, Oates et al. (2013) found that although elderly PD patients implemented similar to controls reactive strategies to stop on an unexpected slippery surface, they showed reduced reactive adaptability (i.e. reduced antero-posterior margin of stability) to planned and not planned stops even after repeated exposure to the perturbation (Oates et al., 2013). Nevertheless, these results are again difficult to interpret because PD patients walked significantly slower than controls, which has a large effect on the magnitude of the perturbation, not allowing objective comparison of the adaptive responses between groups. Tunik et al. also observed impaired reactive adjustments in PD patients in a hand reaching movement when a sudden movement perturbation was induced. Dopamine medication improved their motor performance but could not improve their reaction to the sudden perturbation (Tunik et al., 2007). Furthermore, Paul et al. (2013) also reported deficits in the reactive adjustments to external perturbations using the pull test and related them to the prevalence of falls in PD patients (Paul et al., 2013).

However, most of the studies regarding PD-related adaptation have been made using visuo-motor tasks, such as reaching or hand movements (Tunik et al., 2007; Mongeon et al., 2013; Semrau et al., 2014) or during split-belt treadmill walking, where the main outcome variables were related to gait asymmetry (Dietz et al., 1995; Roemmich et al., 2014). Very little research has been done regarding adaptive strategies to an over ground perturbation of dynamic stability in PD patients and nothing has been reported regarding this topic in young PD patients.

1.3.5 Cognitive factors

PD is associated with a variety of cognitive impairments, including executive function, attention, memory, language, and visuospatial impairments (Muslimovic et al., 2005; Watson and Leverenz, 2010) that could contribute to locomotor deficits, especially in dual-task conditions. Cognitive profiles in PD are variable (Kehagia et al., 2010) and range from mild deficits in specific cognitive domains to severe dementia affecting multiple domains. It is estimated that 19–30% of people newly-diagnosed PD may have cognitive impairments (Muslimovic et al., 2005; Elgh et al., 2009), and these impairments worsen with disease progression (Muslimovic et al., 2007). Cognitive impairments may increase the risk of falling by limiting the ability to compensate for gait deficits using cognitive strategies. Also, impaired executive function might result in the inappropriate or unsafe prioritization of tasks when walking under dual-task conditions. Bloem et al. proposed that increased fall risk in people with PD may result in part from a "posture second" prioritization strategy, in which concurrent tasks are prioritized above walking (Bloem et al., 2001b; Bloem et al., 2006). Consistent with this idea, falls in PD have been associated with reduced performance on a variety of cognitive measures (Allcock et al., 2009; Camicioli and Majumdar, 2010). PD fallers had lower scores in executive function and attention (Dubois and Pillon, 1997; Denney et al., 2014) compared to PD non-fallers. However general measures of cognition, e.g., memory, presented no differences between PD fallers and non-fallers.

Nevertheless, since most PD patients are diagnosed at an age above 60-65 years, the prevalence of cognitive impairments may be more related to the age factor than to the disease (Ludin and Ludin, 1989). The prevalence of cognitive impairments may play a minimal role in young patients.

1.3.6 Sensorimotor deficits

Another important factor responsible for the increased risk of falls in PD patients may be impairments in the sensory system. Sensory information plays a dominant role in the maintenance of dynamic stability during locomotion since reactive postural responses to stability disturbance are based on input from all major sensory systems: vision, vestibular, and kinesthetic (Patla, 2003). These responses rely on recognition of altered task demands and are inefficiently adapted in PD when the context of the disturbance changes since they are highly dependent on the accuracy of the sensory information, which may be compromised in PD patients (Hall et al., 2013). Several deficits in sensory processing have been observed in PD including visual (Armstrong, 2008), limb proprioception (Konczak et al., 2007) and sensorimotor integration (Almeida et al., 2005).

It has been shown that PD patients have a tendency to overestimate the maximum distance they can reach forwards without losing balance (Kamata et al., 2007). Somatosensory deficits in Parkinson`s disease may lead to an abnormal perception of body position, resulting in an overestimation of the

limits of stability and therefore contributing to an increased risk of falling (De Nunzio et al., 2007; Kamata et al., 2007; Allen, 2010).

Other reports have found deficits in axial kinesthesia and related them to the functional impairments of posture and locomotion in PD (Wright et al., 2010) and to the reduced accuracy of their reactive responses (Klockgether et al., 1995). This may happen due to altered peripheral input, increased fusimotor drive, or abnormal processing of kinesthetic information in the basal ganglia. It has been proposed that the primary reason for disturbed function in PD may lie in the changes in the gating and integration of sensory input, which then affect motor output (Abbruzzese and Berardelli, 2003; Konczak et al., 2009).

The basal ganglia then appear to play a role in the integration of sensorimotor information across multiple sensory domains (Jobst et al., 1997; Nowak and Hermsdorfer, 2006). Thus, it is rational to think that dysfunction of these neural circuits in conditions like Parkinson's disease may contribute to impaired sensorimotor integration (Abbruzzese and Berardelli, 2003; Paquet et al., 2008) required for modulating automatic postural reactions, like protective stepping responses to avoid falls (Lee et al., 2013). In contrast, PD patients may use visual feedback to facilitate various aspects of movement and compensate these impairments in other areas of the sensory system (Klockgether and Dichgans, 1994; Brown et al., 2006).

1.4 The effect of exercise interventions on the symptomatic of Parkinson`s disease

Already in 1961, Doshay found less severe disability in PD patients who practiced physical activity (Doshay, 1961). In this paragraph the possible reasons behind this theory with regards to physiological changes in the brain are reviewed as well as the current research on exercise interventions aiming to reduce falls in PD.

1.4.1 General effects of exercise and rehabilitation on the brain in Parkinson`s disease

Very few well-controlled prospective studies have documented the benefits of physical activity in PD patients (Comella et al., 1994; Toole et al., 2000). Recent work with animal models with PD, stroke, and spinal cord injury indicates that rehabilitative training can stimulate a number of plasticity-related events in the brain and the spinal cord, including neuronal outgrowth,

neurotrophic factor expression, synaptogenesis, and even neurogenesis (Jones and Schallert, 1994; van Praag et al., 1999). These use-dependent events, in turn, enhance the range of self-regulated movements that may contribute to a greater plasticity and improved behavioral outcome. Moreover, during slow degeneration of nigrostriatal dopaminergic neurons, coapplication of intense sensorimotor training appears to be neuroprotective (Hirsch et al., 2003).

Exercise training increases the level of neurotrophic factors in the brain, like vascular endothelial growth factor (VEGF) and glia derived neurotrophic factor (GDNF) (Al-Jarrah, 2013), which have been shown to have neuroprotective effects through the enhancement of dopaminergic neural survival (Bowenkamp et al., 1996; Duarte et al., 2012) and to play a part in the neurogenesis of those cells (Yasuhara et al., 2004; Love et al., 2005). Supporting these reports, Gill et al. delivered GDNF directly into the putamen of five PD patients and observed significant improvements of dopamine uptake and storage, as well as of functional locomotion (Gill et al., 2003).

Furthermore, physical activity diminishes inflammation, elevates agents involved in immunomodulatory function (Archer et al., 2011; Wu et al., 2011) and reduces oxidative stress, all of which act as protection for the PD-related neuroinflammation and mitochondrial protein damage (Bloomer et al., 2008; Patki and Lau, 2011).

An improvement to the flow of blood to the brain as a direct consequence of exercise has functional importance not only for promoting the survival of dopaminergic neurons by providing more oxygen and nutrients, but also by making drug delivery more efficient, since a large proportion of levodopa medication does not reach the brain because it is rapidly converted into dopamine. Exercise also induces a significant endogenous synthesis and release of dopamine in the stratium (Al-Jarrah et al., 2007; Muller and Muhlack, 2010), providing the possibility to reduce the intake of anti-parkinsonian medication. This is a very important issue in the treatment of PD since levodopa as a “golden standard” in PD medication results in levodopa-resistance or levodopa-toxicity after 5-7 years of treatment (Al-Jarrah, 2013; Hung and Schwarzschild, 2013), and specially in early-onset PD it has been related to very incapacitating symptoms like early dyskinesias, dystonia and motor fluctuations (Wickremaratchi et al., 2009a). Indeed studies have shown that intense rehabilitation programs lead to a reduction in daily medication dosage in PD (Frazzitta et al., 2011), placing exercise therapy approaches almost at the same impact level as pharmacological therapy in PD (Al-Jarrah, 2013).

1.4.2 Exercise interventions aiming to reduce falls and the fall risk in PD

Interventions to reduce postural instability and falls in PD patients range from whole-body vibration and progressive tango training to more traditional forms of exercise, such as body weight support, treadmill training and lower extremity strengthening (Dibble et al., 2009b). While it is well

documented that exercise can reduce falls in the general older population (Sherrington et al., 2008; Gillespie et al., 2009), there is no such evidence in Parkinson's disease patients (Allen, 2010). There is moderate evidence that physical activity and exercise will result in improvements in postural stability in persons with mild to moderate PD (Dibble et al., 2009a; Allen et al., 2011). However, it remains unclear whether physical activity and motor training can reduce falls in this population (Protas et al., 2005; Ashburn et al., 2007; Dibble et al., 2009a; Allen et al., 2011).

High-intensity resistance training in PD has been shown to improve not only muscle strength (Scandalis et al., 2001; Hirsch et al., 2003; Dibble et al., 2006; Dibble et al., 2009b), but also functional abilities like gait velocity (Scandalis et al., 2001; Dibble et al., 2009b), stride length (Scandalis et al., 2001), stair descent time (Dibble et al., 2006), Timed Up and Go time (Dibble et al., 2009b) and 6-minute walk test distance. Furthermore, the combination of resistance training and balance training has been reported to improve balance to a greater extent in PD patients (Hirsch et al., 2003). These findings suggest that muscle strength training may play an important role in the prevention of falls (Pang and Mak, 2009; Allen, 2010), having a bigger impact if the training intensity is suitably high (Falvo et al., 2008; Hirsch, 2009). However, there are no studies confirming a relation between isolated strength training and a reduced rate of falls in PD patients.

To date, only few published randomized controlled trials have reported on the effect of exercise on falls in PD patients (Protas et al., 2005; Ashburn et al., 2007; Nieuwboer et al., 2007; Allen et al., 2010a; Smania et al., 2010). While two of these showed a reduction in the falling rate using perturbed treadmill walking (Protas et al., 2005) and balance training (Smania et al., 2010), Ashburn et al. reported only a trend towards lower fall rates after a broad range of exercises (including strengthening, range of movement, balance and walking exercises as well as strategies to reduce falls) (Ashburn et al., 2007). Furthermore, the studies from Nieuwboer et al., Harro et al. and Allen et al. found no significant effect on falls or fall rates after different training programs, including rhythmic cued walking (Nieuwboer et al., 2007; Harro et al., 2014), muscle strengthening, balance and cueing strategies to reduce freezing (Allen et al., 2010a). There is, therefore, no consensus as to the most effective form of exercise to address balance impairment in people with Parkinson's disease (Allen et al., 2010a).

A meta-regression showed a greater effect of exercise on balance-related activity performance if highly challenging balance training was included. Exercise that specifically involves movement of the center of mass, narrowing of the base of support and minimizing upper limb support may produce the best results. A higher intensity and volume of training would then be recommended to achieve a consolidated improvement in postural stability in PD (Allen et al., 2011).

Many of the intervention studies use multidimensional training programs rather than directly addressing postural instability in their interventions. The lack of task-specific training is due to our limited understanding of the critical factors responsible for postural instability in PD (Dibble et al., 2009a). Especially in young PD patients with early-onset disease, there is very little information

about the underlying mechanisms contributing to the high prevalence of falls. Identifying these mechanisms without the influence of contaminating factors, like natural age-related balance degeneration, would lead to more targeted, effective and successful interventions aiming to reduce the high risk of falls already at a young age and early stages of the disease.

Another important consideration is whether appropriate outcome measures are being used in these intervention studies. Although biomechanical measures of sway or clinical balance tests may be the easiest measurements to gather, they represent only one potential contributor to potential falls in PD patients. While many of the characteristics of PD postural instability have been described using kinematic, kinetic and electromyographic measures during reactive and anticipatory postural tasks (Hass et al., 2005; Horak et al., 2005), such outcomes and tasks are absent in most of the intervention studies (for more details see the review from Allen, 2011). For these reasons, insight into the mechanisms responsible for the improvements in postural stability has not been clearly given. In the future, intervention studies should include specific biomechanical measures characteristic of PD postural instability (Horak et al., 2005; Dibble et al., 2009a) and, in the case of young patients, characteristic of early-onset PD.

2. Purpose of the thesis

Parkinson`s disease affects 0.3% of the total population, which means that more than 630,000 people are presently diagnosed with PD only in the USA (Kowal et al., 2013), 10% of whom are diagnosed before the age of 51 years (defined as early-onset patients) (Golbe, 1991). The disease is associated with a substantial reduction of independent movement and quality of life, as well as very high costs for the health care system. One of the most disabling symptoms of Parkinson`s disease is postural instability and related falls, which affect more than two-thirds of PD patients (Bloem et al., 2001a; Wood et al., 2002), resulting in severe injuries, disability and costly long-term hospitalization (Temlett and Thompson, 2006). It has been reported that if any treatment or therapy could make the symptoms of the disease progress only 20% more slowly, the economic burden of PD would be reduced by around 25%, which would represent more than $47 billion only in the USA (Johnson et al., 2013). However, despite advances in anti-parkinsonian treatments, drug and surgical therapies seem not to cure or shorten the duration of the disease (Rascol et al., 2003; Savitt et al., 2006). There is no therapy which can really improve all the motor symptoms of PD, and especially postural instability and falls do not seem to be prevented by pharmacological or surgical treatment (Grimbergen et al., 2004; Hall et al., 2013). In the case of early-onset patients, pharmacological therapy is often associated with very disabling motor side effects, like motor fluctuations and dyskinesia (Schrag et al., 2003; Wickremaratchi et al., 2009a). Therefore, the development of exercise-based therapies seems to be a good alternative for reducing the risk of falling in PD patients, thus improving their quality of life. Although there have been some attempts to find effective training therapies to reduce the falling rate in PD, there is still no conclusive evidence on which kind of physical activity would be optimal to reduce falls in this population. The lack of task-specific training interventions is due to our limited understanding of the underlying mechanisms contributing to postural instability and falls in PD (Dibble et al., 2009b), and particularly in early-onset PD patients. Identifying these mechanisms without the influence of contaminating factors, not related to the intrinsic disease process, would lead to more economical, effective and successful interventions. Aging is one of the most relevant contaminating factors related to falls in PD due to the well-known natural age-related balance degeneration. However, since the mean age of PD onset is over 65 years, it is very difficult to recruit suitable patients who are not affected by the effects of aging. Therefore, there is insufficient research on the factors responsible for the reduced stability performance and the increased risk of falls in young (< 58 years old, with disease onset before the age of 51) faller and non-faller PD patients.

In order to allow primary prevention and to prescribe effective targeted interventions, those patients at risk of falling must first be identified within the general population (Bloem et al., 2001a; Bruijn et al., 2013). It is, therefore, necessary to develop more effective assessing methods that allow for early discrimination of individuals at risk of falling, which are sensitive to and specific for young patients as well as early stages of the disease, as well as related to the underlying disease process.
Therefore, the main purposes of this thesis were to:

a) Identify the underlying factors responsible for the disease-specific increased risk of falling in young PD patients with early-onset disease.
b) Develop an adequate instrument for the early identification of PD patients at a high risk of falling, which may be sensitive to young patients and early stages of the disease.

More precisely, we intended to create an integrated research approach focusing on function specific capacities of the human system (i.e. neuromuscular and sensory-motor capacities) and generic motor control potentials under active conditions (i.e. dynamic stability control, locomotor adaptation), aimed to identify risk parameters of falling and to help develop fall prevention strategies in young patients with Parkinson`s disease (on average ~ 48 years old and onset before the age of 51 years).
With regard to the outlined deficits in the research of fall risk factors related to PD, we identified the more relevant factors susceptible to being responsible for the increased falling rate in young PD patients and chose these for investigation. The conducted studies within the present doctoral thesis pursued the following objectives:
The purpose of the first study was to investigate the possible contribution of central factors (i.e. activation deficit of the agonist muscles – quadriceps femoris and triceps surae – and co-activation of the antagonist muscles – hamstrings and tibialis anterior) to muscle weakness of the knee extensor and plantar flexor muscle groups in young faller and non-faller PD patients compared to healthy matched controls. We hypothesized a reduction of muscle strength in PD patients compared to a matched healthy control group and a higher contribution of the central factors in the young Parkinson fallers.
The purpose of the second study was twofold: 1) to investigate the effect of muscle strength and balance ability on dynamic stability control after simulated forward falls as well as on the incidence of real falls (PD fallers vs PD non-fallers) in young PD patients, and 2) to develop an applicable tool to classify early-onset PD patients into fallers and non-fallers. We hypothesized that young PD fallers would present a lower stability performance during simulated forward falls compared to healthy controls, which would be related to decreased muscle strength and balance ability.
Finally, the third study aimed to investigate the effect of unexpected gait perturbations on dynamic stability control in young PD patients compared to age-matched healthy controls, and to examine

the reactive and predictive adaptability following repeated exposure to the perturbation. We hypothesized less stable walking, greater consequences on stability after an unexpected perturbation and lower predictive as well as reactive locomotor adaptability in PD patients.

3. First study:

Central factors explain muscle weakness in young fallers with Parkinson's disease

Authors:

María Moreno Catalá[1]

Dirk Woitalla[2]

Adamantios Arampatzis[1]

[1] Department of Training and Movement Sciences, Humboldt-Universität zu Berlin

[2] Department of Neurology, St. Joseph Hospital, Ruhr-Universtität Bochum

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3.1 Abstract

Background

Muscle weakness in old Parkinson`s disease (PD) patients has been shown to impair their mobility, although the specific origin of this weakness and its relation to falls has not been well examined in young patients.

Objective

This study aimed to analyse the possible contribution of central factors to muscle weakness of the triceps surae and quadriceps femoris muscles in young faller and non-faller PD patients.

Methods

Twenty-six young PD patients (fallers, n=13 and non-fallers, n=13) and 15 matched healthy controls performed several isometric maximal voluntary knee extension and plantar flexion contractions (MVC) of the most affected leg on a dynamometer. We estimated the maximal resultant agonist moments, the antagonistic moment of hamstrings and tibialis anterior during MVCs and the activation deficit of the quadriceps femoris and triceps surae muscles.

Results

Only the Parkinson fallers showed significant lower muscle strength, higher antagonistic moments and higher activation deficit compared to controls. Multiple regression analysis showed that the antagonistic moments and the activation deficit explained about 39% and 27% of the variance in the maximal resultant moments of the knee extensors and the plantar flexors.

Conclusions

Our findings suggest that Parkinson fallers are affected by strength impairments arising from the central nervous system and not from the peripheral muscle contractile capacity, even at early stages of the disease and young age, increasing the risk of falls. High-intensity resistance training in young PD patients may help to enhance neural drive as well as to decrease unwanted antagonistic moments and reduce the falling risk.

Key Words:

Parkinson`s disease, muscle strength, falls, activation deficit, antagonistic moment, early-onset

3.2 Introduction

In patients with Parkinson's disease (PD) the neuromuscular system becomes faulty mainly because of the degeneration of dopaminergic neurons in nigrostriatal systems (Moore et al., 2005). Although Parkinson's disease is generally considered to be a disorder of the elderly, it also affects a substantial number of younger individuals. The mean age of onset is around 65 years, although 5–10% of cases, classified as early-onset, begin below the age of 51 (Marder et al., 2010). The primary symptoms in this disease have a dramatic impact on the patient's mobility and quality of life; postural instability and falls are among the most incapacitating features of Parkinson's disease (Bloem et al., 2001a). Several studies have analysed the rate of falling in Parkinson patients. They reported that 50% to 68% of PD patients fell at least once in the previous year (Bloem et al., 2001a; Wood et al., 2002), and 13% of them fell more than once a week (Nocera et al., 2009). About 42% of the patients suffered injurious falls (Bloem et al., 2004b). Despite advances in pharmacological treatments and surgical techniques, gait and balance deficits still persist and are associated with loss of independence, immobility and high cost for healthcare systems (Tomlinson et al., 2012).
Intrinsic neuromuscular properties of the muscle-tendon unit (MTU) have been shown to influence the function and performance of the entire musculoskeletal system during locomotion (Bassey et al., 1992; Karamanidis and Arampatzis, 2007). The capacity of the human system to generate rapid force for balance corrections after sudden perturbations during locomotion is especially affected by muscle strength and tendon stiffness (Karamanidis et al., 2008). Decreased strength has been reported to be a factor contributing to increased falling in the elderly (Karamanidis et al., 2008; Pijnappels et al., 2008b). It has been reported that elderly PD patients have shown reduced muscle strength (Inkster et al., 2003; Nocera et al., 2009), decreased rate of force development (Paasuke et al., 2002), impaired ability to maintain constant force as well as increased muscle co-activation during balance perturbation tasks (Horak et al., 1996; Dimitrova et al., 2004). The above mentioned weakness in muscle capacities related to several mobility tests like, the chair-rising test (Paasuke et al., 2002) or the time up and go test (Kerr et al., 2010). Recently Latt et al. (2009) reported that muscle weakness in older PD patients was one of the four main independent risk factors for falls. They developed (Latt et al., 2009) an explanatory model using muscle weakness as a factor which correctly classified 77% of the fallers and 82% of the non-fallers between the patients of their study (Latt et al., 2009a). However, the majority of the reported information about muscle weakness in PD patients resulted from studies investigating old participants (between 65 and 85 years old). The Parkinson related decrease in muscle strength may result from both central (i.e. arising from the central nervous system) as well as peripheral factors (i.e. occurring distal to the neuromuscular junction) (Pijnappels et al., 2008a; Nocera et al., 2009). To our knowledge there is no study

investigating the contribution of central and peripheral factors to the reported muscle weakness in young PD patients.

The muscles of the lower extremities (i.e. triceps surae and quadriceps femoris) are very important during locomotion and their strength significantly affect the risk of falling (Pijnappels et al., 2005b) as well as the ability of humans to regain balance after disturbances during walking (Pijnappels et al., 2008b). Therefore, the purpose of this study was to investigate the possible contribution of central factors (i.e. activation deficit of the agonist muscles – quadriceps femoris and triceps surae – and co-activation of the antagonist muscles – hamstrings and tibialis anterior) to muscle weakness of the knee extensor and plantar flexor muscle groups in young faller and non-faller PD patients (39 – 57 years old) comparing them to healthy matched controls. We hypothesised a reduction of muscle strength in PD patients compared to a matched healthy control group and a higher contribution of the central factors in Parkinson fallers.

3.3 Methods

3.3.1 Participants

Fifteen healthy adults and twenty-six patients with early-onset idiopathic PD (in the I – III stage of the H&Y Parkinson scale) have been recruited for the study (Table 3.1). The Parkinson Patients were divided into two groups (non-fallers, n=13 and fallers, n=13). The non-faller group included patients with no fall experience in the last six months and the faller group included patients who have experienced more than one fall in the last six months. A fall was defined as "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects" (World-Health-Organization, 2007). A history of any other neurological or orthopedic disorder that could affect their ability to perform a maximal contraction was considered as exclusion criteria for participating in this study. The patients were included in the study if they did not meet these exclusion criteria. Individuals were examined during the ON phase, when they self-reported that their medications were working optimally, about 30 minutes to 1 hour after they had taken their usual dose of antiparkinsonian medication. The control group was matched to the Parkinson group regarding age, anthropometrical parameters (weight and height) and sport activity. Sport activity was quantified as hours per week of regular sport activity practiced in the past year and was estimated using a questionnaire enquiring the type of sport activity, frequency of practice (i.e. hours per week and weeks per year) and intensity of the activity.

The study has been approved by the university ethics committee and the participants gave informed consent to the experimental procedure.

Tab. 3.1 Anthropometric data, age at disease onset and stage in the Hoehn & Yahr Parkinson (H&Y) scale for the three groups (means ± standard deviation).

	Controls (n=15)	**Parkinson non-fallers** (n=13)	**Parkinson fallers** (n=13)
Age [yr]	48 ± 5	47 ± 6	49 ± 5
Body mass [kg]	79.2 ± 15.1	82.4 ± 19.7	72.4 ± 11.3
Body height [cm]	174 ± 11	175 ± 9	169 ± 8
Body mass index [kg/m²]	25.6 ± 4.6	27.2 ± 4.7	25.3 ± 3.2
Age at disease onset [yr]		42 ± 5	43 ± 6
H&Y scale		1.8 ± 0.8	2.1 ± 0.8

There were not statistical differences ($p>0.05$) in any of these parameters between the three groups.

3.3.2 Measurement of the muscle strength and EMG-activity

After an initial warm-up consisting of several submaximal and two to three maximal contractions, the participants performed several isometric maximal voluntary knee extension contractions (MVC) and ankle plantar flexion contractions with the most affected leg (the one where the symptoms appeared at first). For the knee extension they were seated with a hip angle set at 140º and knee angles set at 105º, 110º, 115º and 120º. A straight position at the hip and knee joints corresponded to a 180° joint angle. For the plantar flexion the knee angle was set at 180° and ankle angles at 75°, 80°, 85° and 90º. The foot perpendicular to the tibia corresponded to an ankle joint angle of 90°. Different joint angle configurations were chosen in order to examine triceps surae (TS), i.e. soleus, gastrocnemius medialis and lateralis, and quadriceps femoris (QF), i.e. rectus femoris, vastus lateralis, medialis and intermedius, muscle strength potential near to the optimal individual joint angle. For the statistical analysis we used the highest value within the contractions. The different joint angle configurations were applied in random order where a three-minute rest between the contractions was allowed.

We used an inverse dynamic approach to calculate the resultant moments at the knee and ankle joints. With this approach we corrected the moments measured by the used dynamometer (Biodex Medical Systems Inc., USA) by rectifying the misalignment of the dynamometer and joint axis during the contractions (Arampatzis et al., 2004; Arampatzis et al., 2005). For that, kinematic data were recorded using the Vicon 624 system (Vicon Motion Systems, Oxford, UK) with 11 cameras operating at 120 Hz. Reflective markers were fixed on the tuber calcanei, lateral and medial

malleolus, lateral and medial femoral condyles, trochanter major, lateral aspect of the spina iliaca, axis of the dynamometer and on the dynamometer arm at the point of force application to define the distance between the line of action of the exerted force and the axis of rotation of the dynamometer lever. The exact method has been previously described (Arampatzis et al., 2004; Arampatzis et al., 2005).

To assess the contribution of the antagonist muscles (i.e. co-activity) to the examined maximal resultant joint moment we calculated the moments of the antagonist hamstrings (HA) and tibialis anterior (TA) muscles during knee extension and plantar flexion MVCs. For that the antagonist EMG-activity of HA and TA was recorded using autoadhesive preamplified electrodes during the MVCs. The electrodes were positioned above the midpoint of the muscle belly of TA and of biceps femoris muscle as a representative of the HA muscles. The inter-electrode distance was 2 cm and electrodes were placed parallel to the presumed direction of the muscle fibers. The antagonistic moment of HA and TA was then estimated by establishing a relationship between the EMG amplitude and the exerted moment for HA and TA whilst working as agonist (Baratta et al., 1988; Mademli et al., 2004). Therefore, the EMG activity of the HA and TA and the corresponding moment were measured in three additional trials: (a) in relaxed state, (b) producing knee flexion and dorsiflexion contractions displaying an EMG amplitude of the HA and TA below the maximum amplitude measured during knee extension and plantar flexion and (c) a second knee flexion and dorsiflexion contractions where the EMG amplitude was slightly above the maximum amplitude registered during the knee extension and the plantar flexion. The moments measured in each of the three trials were fitted by a linear regression curve as function of the corresponding EMG values of the HA and TA. This allowed the estimation of the antagonistic moment during the MVCs. This method is only valid under the condition that the neuromuscular activation is the only factor determining the force generating potential. We assured this condition by keeping the muscle length constant (i.e. at a given joint angle) and the muscle shortening velocity equal to zero (i.e. isometric contractions) during the trials. The co-activation level was defined as the antagonistic moment of HA or TA muscles during the knee extension or plantar flexion MVCs normalised to the maximal exerted knee extension or plantar flexion resultant moment respectively.

3.3.3 Assessment of the voluntary activation

For the assessment of the voluntary activation during the maximal isometric knee extension and ankle plantar flexion contractions we used the twitch interpolation method (Merton, 1954). Two carbon rubber electrodes (5.5x10 and 5.5x9 cm), thinly coated with conductive adhesive gel, were secured onto the skin. For the QF the cathode was placed on the proximal anterior thigh, and the anode was placed over the motor point area of the muscles rectus femoris and vastus lateralis. For the TS the cathode was above the midway between the two heads of gastrocnemii and

approximately 5 cm distal to the crease in fossa poplitea, and the anode above the soleus' motor point, along the medial line directly below the belly of medial and lateral gastrocnemius muscles. Each muscle group was stimulated transcutaneously with triplet twitches (square-wave pulses of 500 ms at 200 Hz) by means of a constant-current stimulator (Digitimer DS 7A, Welwyn Garden City, Herdfordshire, UK) at the plateaus of knee extension and plantar flexion contractions as well as at the subsequent resting phases. The current of the twitches was determined in a previous test by successively increasing the current until the maximal rest twitch torque was evoked. This current plus 20% was used during the stimulation trials. Triplet twitches were used instead of single ones in order to increase the duration of the elicited contraction and this way minimise the influence of tendon compliance on muscle force production. It has further been reported that the multiple twitches decrease the variability of muscle responses (Suter and Herzog, 2001). The stimulator delivered a TTL output signal (0–5 V) simultaneous to the twitch, which was registered by the Vicon unit to synchronise the systems. Activation deficit was calculated by normalising the evoked interpolated twitch torque (ITT) (Schott et al., 2007) to the subsequent resting twitch torque (RTT), Activation deficit = (ITT/RTT) x 100.

3.3.4 Statistics

A two-way analysis of variance was used to check the muscle group (QF, TS) and participant group (controls, Parkinson non-fallers, Parkinson fallers) related differences in the examined parameters (i.e. maximal resultant moment, moment of the antagonists and activation deficit). When significant participant group differences were detected, a post-hoc test (Bonferroni) was applied in order to determine where these differences occurred. Further, we conducted a multiple regression analysis to determine whether the activation deficit of the agonists (QF and TS) and the co-activity of the antagonist muscles (HA and TA) might predict the achieved plantar flexion and knee extension moments. The level of significance was set at $\alpha = 0.05$.

3.4 Results

The two-way analysis of variance revealed statistically significant ($p<0.05$) muscle group effects in the resultant moment and in the moments of the antagonistic muscles, but not in the activation deficit (Tables 3.2, 3.3 & 3.4). The maximal resultant knee joint moments were higher ($p<0.05$) compared to the maximal plantar flexor moments in all three participant groups, as well as the moments of the antagonist muscles HA compared to TA. The Parkinson faller group revealed

significantly ($p<0.05$) lower maximal resultant knee extension as well as lower maximal resultant ankle plantar flexion moments compared to the control group (Table 3.2). However, the Parkinson non-fallers did not show any statistically significant differences ($p>0.05$) in the maximal knee extension and plantar flexion moments compared to the other two groups (Table 3.2). In a similar way the moments of the antagonists HA and TA showed significantly higher values ($p<0.05$) only between the control and the Parkinson faller group (Table 3.3). Furthermore, the activation deficit in both muscle groups (knee extensors and plantar flexors) was significantly higher ($p<0.05$) in Parkinson fallers compared to controls (Table 3.4).

The multiple regression analysis revealed a significant influence of the two predictor variables (moment of the antagonists HA and TA and activation deficit of QF and TS) on the maximal resultant moments of the knee extensors ($F = 9.742$, $p = 0.001$, $R = 0.627$) and the plantar flexors ($F = 4.114$, $p = 0.03$, $R = 0.522$).

Tab. 3.2 Maximal resultant knee extension joint moment ($Moment_{Knee}$) and maximal resultant ankle plantar flexion moment ($Moment_{Ankle}$) normalised to body weight by the three examined groups (mean ± standard error of mean and coefficient of variation in parentheses)

Muscle group	**Controls** (n=15)		**Parkinson non-fallers** (n=13)		**Parkinson fallers** (n=13)	
$Moment_{Knee}$ (Nm/kg)[#]	2.57 ± 0.15[*]	(0.23)	2.45 ± 0.10	(0.25)	2.22 ± 0.16[*]	(0.15)
$Moment_{Ankle}$ (Nm/kg)[#]	2.12 ± 0.14[*]	(0.23)	1.89 ± 0.09	(0.28)	1.63 ± 0.13[*]	(0.16)

***** Significant participant effect, $p < 0.05$. The post-hoc comparisons showed significant ($p < 0.05$) differences only between the control and the Parkinson faller groups.
[#] Significant muscle effect, $p < 0.05$.

Tab. 3.3 Moment of the antagonist muscles hamstrings and tibialis anterior during the maximal knee extension and plantar flexion contractions. The values are normalised to the maximal resultant knee extension and ankle plantar flexion moments (mean ± standard error of mean).

Muscle group	**Controls** (n=15)	**Parkinson non-fallers** (n=13)	**Parkinson fallers** (n=13)
Hamstrings (%)[#]	4.76 ± 0.69*	8.00 ± 1.40	9.91 ± 1.73*
Tibialis anterior (%)[#]	1.93 ± 0.20*	3.21 ± 0.96	5.57 ± 2.44*

***** Significant participant effect, $p < 0.05$. The post-hoc comparisons showed significant ($p < 0.05$) differences only between the control and the Parkinson faller groups.
[#] Significant muscle effect, $p < 0.05$.

Tab. 3.4 Activation deficit of the quadriceps femoris and triceps surae muscles during the maximal knee extension and plantar flexion contractions (mean ± standard error of mean).

Muscle group	Controls (n=15)	Parkinson non-fallers (n=13)	Parkinson fallers (n=13)
Quadriceps femoris (%)	8.99 ± 1.65*	15.83 ± 2.39	14.39 ± 2.35*
Triceps surae (%)	6.75 ± 2.85*	9.28 ± 3.24	17.61 ± 4.91*

* Significant participant effect, $p < 0.05$. The post-hoc comparisons showed significant ($p < 0.05$) differences only between the control and the Parkinson faller groups.

3.5 Discussion

Differences in muscle strength between old Parkinson patients (>65 years old) and healthy matched controls are reported by the majority of studies using maximal isometric contractions (Pedersen and Oberg, 1997; Robichaud et al., 2004). This muscle weakness in old Parkinson patients has been related to performance deficits by several functional and clinical tests showing an increased risk of falls in this population (Schilling et al., 2009). Recent studies reported that the reduction of maximal muscle strength is the major determinant of reduced muscle power in Parkinson patients, while other factors like bradykinesia of the lower limbs have a minor contribution (Paul et al., 2012a). This means that maximal muscle strength still remains to be one of the most relevant parameters regarding mobility and stability in Parkinson patients. However, the contribution of central and peripheral factors to the found muscle weakness especially in young Parkinson patients (<58 years old) is not well understood. Knowledge regarding this contribution would be very important for planning effective therapeutic interventions aiming to prevent falls in Parkinson patients. Therefore we investigated the muscle strength, the antagonistic moments and activation deficit during maximal isometric knee extension and plantar flexion contractions in faller and non-faller Parkinson patients (on average ~48 years old) and we compared the values to a matched healthy control group. We found that only the Parkinson faller group showed significantly lower muscle strength, higher antagonistic moments and higher activation deficit within the examined muscle groups compared to the control group, partly confirming our hypothesis.

In order to examine whether the variance in the maximal resultant knee extension and plantar flexion moments in our participants could be accounted for by the antagonistic moment of HA and TA and the activation deficit of QF and TS we used a multiple regression analysis for each response variable (i.e. knee extension and plantar flexion moments) including the two corresponding predictor variables (i.e. antagonistic moment of HA or TA and activation deficit of QF or TS). The antagonistic moment and the activation deficit of the agonists explained about 39%

and 27% of the variance in the maximal resultant moments of the knee extensors and the plantar flexors, respectively. This relationship demonstrates that the reduced muscle strength of the leg extensors in PD patients can be highly accounted for by the increased antagonistic moment and the increased activation deficit of the agonists.

An important finding of the current investigation was the existence of central originated deficits (i.e. increased antagonistic moments and activation deficit of the agonists) in muscle strength in young Parkinson fallers. Assuming similar co-activation moments and activation deficits between the three groups, the achieved joint moments would be more or less similar between the groups indicating no significant contribution of peripheral factors to the found muscle weakness in our young Parkinson patients. Therefore, we can argue that impairments in the neuromuscular capacities already appear at young ages, thus reducing their ability to exploit the entire muscle potential.

The consequences of the found results in the Parkinson fallers may be a decrease in rate of muscle force development (Paasuke et al., 2004), a decrease in postural stability (Horak et al., 1996; Allen et al., 2010b) and a decrease in reactive adjustments to regain balance after perturbations (Dimitrova et al., 2004), increasing the risk of falling. An increase in the co-activation of the antagonist muscles in Parkinson patients during maximal isometric contractions of the upper limb muscles (Glendinning and Enoka, 1994) as well as in the lower limb muscles during balance perturbation tasks (Horak et al., 1996; Dimitrova et al., 2004) has been also reported in literature. It can be argued that the Parkinson fallers were not able to selectively activate only the most effective muscles for a given task already in early disease onset, suggesting an important role of the basal ganglia in optimizing muscle synergy patterns. An increase in muscle co-activation has been shown to decrease the postural control of old participants during quiet stance (Nagai et al., 2011) as well as during downward stepping (Hortobagyi and DeVita, 2000). Furthermore, the higher activation deficit in TS and QF muscles indicates impairments in the ability of Parkinson fallers to utilize the entire muscle potential of the most important muscles for locomotion. A limited capacity to sufficiently generate high knee extension and ankle plantar flexion moments increases the risk of falls (Pijnappels et al., 2008b). Our findings suggest that Parkinson fallers are affected by strength impairments arising from the central nervous system and not from the peripheral muscle contractile capacity, even at early stages of the disease and at a young age, increasing the risk of falls during daily activities.

However, knowing the origin of the impairment, an exercise intervention for muscle strength can be effectively designed and focused on centrally originated factors for muscle weakness. In the literature it has been reported that short-term traditional strength training in healthy populations show significant gains in maximal force production without concomitant muscle hypertrophy (Falvo et al., 2008). It is generally accepted that neural adaptations might be responsible for muscle strength enhancement (Gabriel et al., 2006). Griffin and Cafarelli (2005) reported that an increase

in neural drive observed subsequent to resistance training may reflect adaptations at the level of the central nervous system (Griffin and Cafarelli, 2005). Likewise heavy-resistance training can cause a decrease in the co-activity of the antagonist muscles (Hakkinen et al., 1998) resulting in an increase of the resultant joint moment and thus affecting the effectiveness of functional tasks. Furthermore high-intensity strength training shows beneficial effects in denervated muscles as for example in post-polio syndrome patients (Einarsson, 1991) and amongst the elderly. In old Parkinson patients, improvements in muscle strength and mobility have been reported following strength training. These improvements were greater with those patients who performed high-intensity strength training compared to those who performed traditional resistance strength training (Dibble et al., 2009b). Therefore it can be argued that high-intensity resistance training may be a therapeutic issue for Parkinson patients in order to enhance neural drive to the agonist muscles as well as to decrease unwanted antagonistic moments, which are not efficient for the performance of quick postural corrections. Both may contribute to improve strength and movement control and therefore to prevent falls. Finally, the current results show the necessity of resistance training interventions for young Parkinson patients already in early stages of the disease in order to reduce the risk of falls.

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3.7 Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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4. Second study:

Recovery performance and factors that classify young fallers and non-fallers in Parkinson's disease

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Authors:

María Moreno Catalá[1]

Dirk Woitalla[2]

Adamantios Arampatzis[1]

[1] Department of Training and Movement Sciences, Humboldt-Universität zu Berlin

[2] Department of Neurology, St. Joseph Hospital, Ruhr-Universtität Bochum

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4.1 Abstract

Postural instability is a major problem for Parkinson´s disease patients (PDs). Identifying the causes of postural instability at a young age would contribute to the development of adequate training interventions aiming to reduce falls. The purpose of this study was to investigate the effect of muscle strength and balance ability on dynamic stability control after simulated disturbances and to develop an applicable tool able to classify young PDs into fallers and non-fallers. Twenty-five young PDs (12 fallers, 13 non-fallers, 48±5 yrs.) and 14 healthy controls participated in the study. Dynamic stability was examined during simulated forward falls. Muscle strength was assessed by isometric maximal plantarflexion and knee extension contractions. Balance ability was evaluated by measuring the anterior and posterior limits of stability (LoS). The fallers showed lower recovery performance in forward falls and lower muscle strength compared to controls. Muscle strength and anterior LoS were significantly associated to stability performance. These two factors could correctly classify 90% of PD fallers, establishing an accurate assessment tool to predict the falling risk in young PDs. Furthermore, muscle strength partly explained recovery performance; therefore, we can argue that young PDs with an increased falling risk may benefit from leg-extensors strengthening and stability training.

Key words: Parkinson`s Disease, fall prevention, dynamic stability, early disease onset.

4.2 Highlights

- Young PD fallers show reduced recovery performance after simulated forward falls.
- This deficit is explained by a reduced ability to rapidly increase their base of support.
- PD non-fallers do not show any differences compared to healthy controls.
- Recovery performance is associated to leg extensors` muscle strength and anterior LoS.
- Muscle strength and anterior LoS are a strong predictor of the falling risk in young PD.

4.3 Introduction

Postural instability is one of the primary symptoms in Parkinson`s Disease (PD). Episodes of falls are a direct consequence which has a dramatic impact on patient`s mobility resulting in loss of independence and quality of life (Bloem et al., 2001a). Several studies have analyzed the rate of falling in PD and have reported that up to 68% of patients experienced a fall in the last 12 months. However, posture and balance disorders are not taken into appropriate consideration and are sometimes even ignored at early stages of PD (Guler et al., 2012).

Traditionally, the approach of the center of pressure (CoP) to the limits of stability (LoS) has been used to assess balance in healthy elderly as well as in elderly PD patients (Menant et al., 2011; Shen and Mak, 2012). However, these tests show inconsistent results on fall prediction (Fasano et al., 2012). For example, some studies found an association between the falling rate and functional reach distance or voluntary postural sway (Tucker et al., 2010; Butler et al., 2011), while others could not find any significant difference between fallers and non-fallers (Wallmann, 2001). Since most falls occur during dynamic situations (Tinetti et al., 1988; Rubenstein, 2006), conclusions from investigations about static postural control are not directly transferable to dynamic stability control (Owings et al., 2000; Mackey and Robinovitch, 2005). Nevertheless, there might be a contribution of balance ability (i.e., the ability to approach the CoP to the LoS) to the increased risk of falling in PD patients, though this is still unclear.

Muscle strength of the leg extensors has been shown to significantly affect the recovery performance after sudden perturbations in elderly participants (Arampatzis et al., 2008; Karamanidis et al., 2008; Graham et al., 2013). Postural corrections after a perturbation depend on the actions of both the support limb during the push-off phase and the recovery limb during the step execution phase (Pijnappels et al., 2005b; Karamanidis and Arampatzis, 2007). Furthermore, it has been reported that deficits in using the mechanisms responsible for dynamic stability control affect balance recovery after simulated forward falls in elderly adults (Arampatzis et al., 2008).

There have been some attempts to analyze the impaired recovery performance responsible for the increased risk of falls in PD patients. During gait (Plotnik et al., 2011) and balance perturbation (Nanhoe-Mahabier et al., 2012) tasks, elderly PD patients have presented decreased gait bilateral coordination and greater displacement of the center of mass after perturbations, respectively. Diminished ability to optimize postural response for changes in postural demand has been also reported in PD patients (Dimitrova et al., 2004; Horak et al., 2005). Summarizing, a lot of studies in the past have investigated the specific risk factors for falls in PD in a retrospective (Ashburn et al., 2001a; Robinson et al., 2005; Durmus et al., 2010) as well as in a prospective way (Bloem et al., 2001a; Pickering et al., 2007; Paul et al., 2014). These studies have highlighted impaired

balance, freezing of gait, decreased muscle strength, impaired cognition and disease severity as important factors associated to the higher falling rate in PD. However, all these studies were conducted with elderly patients and their results may not be directly applicable to young PD patients. Since the mean age of disease onset is around 65 years old, it is very difficult to differentiate between the factors intrinsic to the disease and the factors resulting from natural age-related degeneration. New knowledge gained in elderly PD patients is not directly transferable to young PD patients, since it is well known that the ability to control stability deteriorates in healthy elderly, as compared to healthy young adults (Pijnappels et al., 2005a; Karamanidis and Arampatzis, 2007).

Early or young onset PD is defined as Parkinson's disease diagnosed before the age of 51 years (Schrag and Schott, 2006; Marder et al., 2010). Although early-onset PD patients seem to experience motor symptoms similar to normal or late onset patients (Calne and Kumar, 2008), they are characterized by earlier and more frequent motor fluctuations and treatment-related dyskinesia than normal-onset patients (Quinn et al., 1987; Schrag et al., 2003). Both motor fluctuations and dyskinesia are very incapacitating factors which reduce patients` mobility and level of activity. Dystonia, particularly affecting feet and ankles, is also more common in patients with early-onset PD (at the time point of onset as well as during treatment) (Mehanna et al., 2014), and may have an effect on patients' functional performance as well. Especially the greater side effects of the antiparkinsonian medication in early-onset disease (Giovannini et al., 1991), affecting motor symptoms and functionality, highlight the importance of developing alternative non-pharmacological therapies aiming to reduce motor deficits and falls in these young patients.

Currently, there is a lack of studies analyzing stability performance during dynamic situations in young (< 58 years old) faller and non-faller PD patients with early-onset disease. In order to develop appropriate strategies to prevent falls in young PD patients, deeper knowledge in assessing the factors responsible for their postural instability is needed without the influence of the natural age-related balance degeneration. The analysis of the contribution of muscle strength and balance ability on dynamic stability control during balance recovery tasks in PD patients already at this young age would help to develop more effective therapeutic interventions aiming to prevent incidents of falls in young PD patients.

An early identification of patients at a high risk of falling is a crucial factor for primary fall prevention. In this way, a sensitive and easier applicable tool able to predict the risk of falls in young PD patients would improve the effectiveness of fall prevention therapies in this group of patients. Motor performance tests (e.g. retropulsion test) are easy to perform in clinical settings. However, most of the studies aiming to evaluate the sensitivity and specificity of those tests for assessing the risk of falls in PD patients have been conducted with elderly participants (mean age >65) (Leddy et al., 2011b; Duncan and Earhart, 2012). Furthermore, these studies have reported that the strongest predictor for future falls is a previous history of falling, which does not allow any

primary prevention (Ashburn et al., 2001b; Fasano et al., 2012). Thus, it is necessary to develop adequate clinical tests to predict the risk of falling in PD patients, already at a young age and early disease onset, in order to be able to apply strategies aiming to prevent falls in advance, before injurious falls occur.

Therefore, the purpose of this study is two-fold, 1) to investigate the effect of muscle strength and balance ability on dynamic stability control after simulated forward falls as well as on the incidence of real falls (PD fallers vs. PD non-fallers) in young PD patients (on average ~ 48 years old), and 2) to develop an applicable tool able to classify early disease onset PD patients into fallers and non-fallers. We hypothesized that young PD fallers present a lower stability performance during simulated forward falls compared to healthy controls, which is related to decreased muscle strength and balance ability.

4.4 Methods

4.4.1 Participants

The investigation was conducted with fourteen healthy adults and twenty five young patients with idiopathic PD (Table 4.1). The inclusion criteria for this study were as follows: having idiopathic PD as confirmed by a medical practitioner (i.e., patient`s local neurologist), being able to walk independently, having a disease onset before the age of 51 years, and being 58 years old or younger at the time of inclusion. Patients were not included in the study if they had a history of any other neurological or orthopedic disorder or if they were assigned to a stage above 3 of the Hoehn & Yahr scale (Hoehn and Yahr, 1967). PD Patients were divided into two groups: a) PD non-fallers, with no fall experience in the last six months and b) PD fallers, who experienced more than one fall in the last six months. A fall was defined as "inadvertently coming to rest on the ground, floor or other lower level" (World-Health-Organization, 2007). Individuals were examined during the ON phase, when they self-reported that their medication was working optimally, about 30 minutes to 1 hour after they had taken their usual dose of antiparkinsonian medication. The control group was matched to the PD groups regarding age, weight, height and sport activity level. Sport activity was quantified as hours per week of regular sport activity practiced in the past year, which was estimated using a questionnaire. Self-reported motor symptoms were also gathered using a questionnaire. The work was approved by the university ethics committee and all participants gave informed consent to the experimental procedure.

Tab. 4.1 Anthropometric data, age at disease onset, stage in the Hoehn & Yahr Parkinson (H&Y) scale and self-reported motor symptoms for the three groups (means ± standard deviation).

	Controls (n=14)	**PD non-fallers** (n=13)	**PD fallers** (n=12)
Age [yr]	47 ± 5	47 ± 6	49 ± 4
Body mass [kg]	76.9 ± 14.6	82.4 ± 19.7	72.4 ± 11.3
Body height [cm]	175 ± 11	175 ± 9	169 ± 7
Body mass index [kg/m²]	25.9 ± 5	27.2 ± 4.7	25.3 ± 3.2
Age at disease onset [yrs.]		42 ± 5	43 ± 6
H&Y scale		1.8 ± 0.8	2.1 ± 0.8
Tremor [nº of patients]		6	5
Rigor [nº of patients]		7	9
Bradykinesia [nº of patients]		8	6
Freezing [nº of patients]		0	2

There were not statistical differences ($p>0.05$) in any of these parameters between the three groups.

4.4.2 Measurement of the recovery performance

The experimental design of the recovery task has been previously reported in detail (Karamanidis and Arampatzis, 2007). Briefly, the subjects were released suddenly without warning from a fixed forward-inclined position. A horizontal inextensible cable was attached to a belt worn by the participants around the pelvis and could be suddenly released by means of a custom-built pneumatic braking system. Prior to recording, several habituation trials (5-6) were carried out in order to avoid learning or habituation effects (Barrett et al., 2012) during the measurements. The forward lean angle was controlled by adjusting the lean control cable length until the load cell attached to the cable indicated that it supported a specified percentage of the participant's body weight (BW). This angle was adjusted to start from approximately 8–10% BW. The participants were instructed and encouraged to restore balance by taking a single step after the forward fall was initiated. Once the participant was able to successfully perform the task with a single step throughout three attempts, the lean angle was increased by 2–3% BW until the participant could not manage to restore balance with a single step after the forward release. The successful trial with the highest forward inclination was chosen for analysis.

Kinematic data was recorded with 12 Vicon cameras operating at 120 Hz. Twenty-one reflective markers (radius 14 mm) were used to track whole body kinematics (Bierbaum et al., 2013). The segmental masses and the location of the segment centers of mass were calculated based on the data reported by Dempster (Dempster et al., 1959).

To quantify the responses in dynamic stability control during the forward falls we used the "extrapolated center of mass" concept formulated by Hof (Hof et al., 2005). The margin of stability (b_x) as a criterion for the state of stability of the human body was calculated according to:

$$b_x = U_{\max} - X_{CM} \qquad \text{(Eq. 4.1)}$$

where b_x indicates the margin of stability in the anterior-posterior direction, U_{max} is the anterior boundary of the base of support (BS) and X_{CM} is the position of the extrapolated center of mass in the anterior-posterior direction defined as:

$$X_{CM} = P_{XCM} + \frac{V_{XCM}}{\sqrt{g/l}} \qquad \text{(Eq. 4.2)}$$

P_{XCM} is the horizontal (anterior-posterior) component of the projection of the center of mass (CM) to the ground, V_{XCM} is the horizontal CM velocity and the term $\sqrt{g/l}$ presents the eigenfrequency of a system of length l (inverted pendulum model), where g is the acceleration of gravity and l is the distance between CM and center of the ankle joint in the sagittal plane. Postural stability is maintained in circumstances where the position of the extrapolated CM is within the base of support (i.e. $b_x \geq 0$) while stability is lost in cases where the extrapolated CM passes the anterior boundary of the base of support (i.e. $b_x < 0$) (Figure 4.1). Recovery performance was defined as b_x at release of the most unstable forward inclined position that participants were able to recover with a single step.

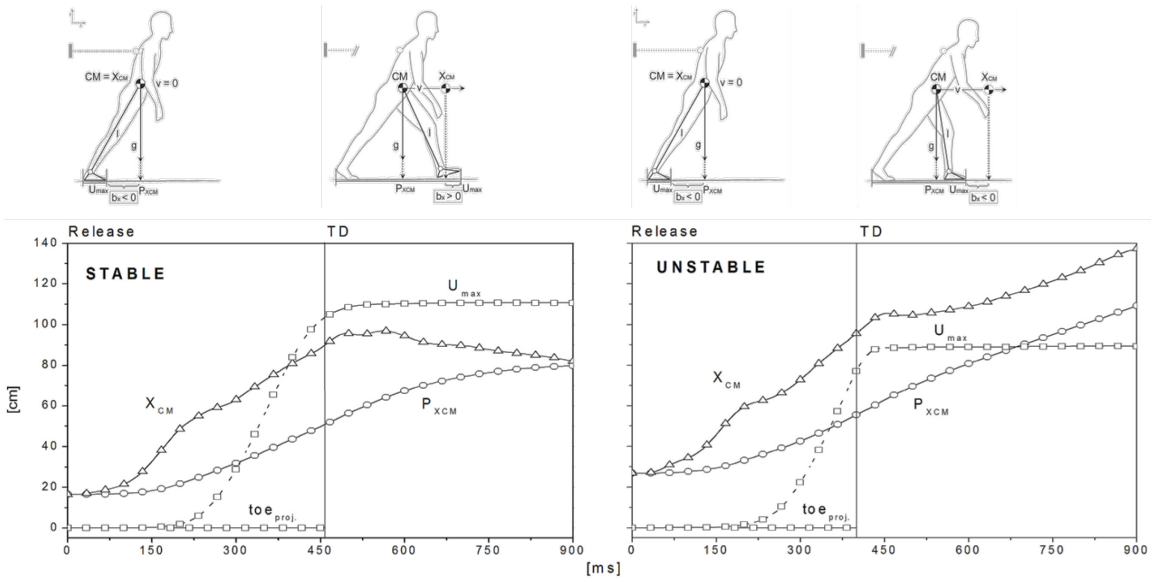

Fig. 4.1 Parameters of dynamic stability.
Anterior boundary of the base of support (U_{max}), horizontal component of the projection of the toe from the recovery limb to the ground ($toe_{proj.}$), horizontal component of the projection of the center of mass to the ground (P_{XCM}), and position of the extrapolated center of mass (X_{CM}) during the forward falls at release and touch down, for a stable (margin of stability (b_x) > 0, recovery with a single step) and an unstable (b_x < 0, no recovery with a single step) trial. Margin of stability is the instantaneous difference between the U_{max} and the $X_{CM.}$

4.4.3 Measurement of muscle strength

To examine muscle strength potential of the leg extensor muscle–tendon units, all participants performed isometric maximal voluntary knee extension and ankle plantarflexion contractions on a dynamometer (Biodex Medical Systems. Inc., USA). The resultant knee extension and ankle plantarflexion moments were calculated through inverse dynamics (Arampatzis et al., 2004; Arampatzis et al., 2005). Axis misalignment between the dynamometer and the ankle or knee joint during the contraction was taken into consideration using 12 Vicon cameras.

4.4.4 Measurement of the balance ability

Balance ability was evaluated by measuring the voluntary approach of the center of pressure (CoP) to the limits of stability (LoS) in both anterior and posterior directions using a force plate. The LoS have been defined as the anterior boundary of the toe and the posterior boundary of the calcaneus of both feet. Participants moved their center of mass forwards and backwards as far as possible without falling while maintaining a stationary base of support and a straight body configuration. The approach of the CoP to the LoS in the anterior and posterior direction was defined as the minimum distance between the maximal voluntary achieved position of the CoP to the boundaries of the toe and calcaneus, respectively.

4.4.5 Statistics

The differences between groups (controls, PD non-fallers and PD fallers) were investigated using a one-way ANOVA and Tuckey post-hoc test. We used the Pearson correlation coefficients to investigate the relationship between muscle strength, balance ability and recovery performance. In addition, in order to identify an easily applicable tool to assess the risk of falling in young PD patients, we performed a discriminant analysis which examined to what extent muscle strength and balance ability could correctly classify the young PD fallers. The level of significance was set at α=0.05.

4.5 Results

4.5.1 Differences between young PD fallers, PD non-fallers and controls

No statistically significant differences were found between the three groups for the anthropometric data or the sport activity level.

Young PD fallers showed a lower ($p<0.05$) recovery performance compared to the healthy controls. The controls were able to recover from a more unstable forward inclined position and therefore from a lower initial b_x at release (-24 cm) compared to the PD fallers (-17 cm). The non-faller PD patients and the control group showed no differences in the recovery performance (Table 4.2). The lower ability to increase the BS after a forward fall was the main deficit responsible for the impaired recovery performance in the PD fallers compared to controls (94 vs 113 cm, respectively) (Table 4.2). At touchdown (TD), PD fallers showed lower values in the horizontal CM projection and horizontal CM velocity as compared to the other two groups, because of the decreased BS and the lower demand of their inclination angle at release (Table 4.2). The consequence was a lower extrapolated CM position at TD than the other two groups (Table 4.2). In a similar way the PD fallers revealed significantly ($p<0.05$) lower maximal isometric knee extension and lower maximal isometric ankle plantarflexion moments when compared to the other two groups, while the PD non-fallers and controls did not show any statistically significant differences ($p>0.05$) (Table 4.2). Both the ability to approach the CoP to the anterior or to the posterior LoS did not show any statistically significant differences ($p>0.05$) between the three groups (Table 4.2).

Tab. 4.2 Maximal isometric knee extension and ankle plantarflexion moments, margin of stability at release, base of support, extrapolated CM, horizontal CM projection and horizontal CM velocity at touchdown from the most inclined single step trial and maximal approach of the CoP to the anterior and the posterior limits of stability (mean ± standard deviation of the mean).

	Controls (n=14)	**PD non-fallers** (n=13)	**PD fallers** (n=12)
$Moment_{Knee}$ (Nm)	203.5 ±69*	204.07 ±63$^{\#}$	159.54 ±45*$^{\#}$
$Moment_{Ankle}$ (Nm)	161.22 ±45*	149.17 ±32$^{\#}$	115.27 ±29*$^{\#}$
Margin of $stability_{release}$ [cm]	-24.05 ±5.7*	-21.63 ±5.6	-17.2 ±6.4*
Base of $support_{TD}$ [cm]	112.71 ±10.3*	106.915 ±20.8	94.09 ±11.9*
Extrapolated CM_{TD} [cm]	109.86 ±11.4*	101.46 ±18.9	89.44 ±13.8*
Horizontal CM $projection_{TD}$ [cm]	66.48 ±7.9*	60.59 ±12.0	52.54 ±9.2*
Horizontal CM $velocity_{TD}$ [m/s]	1.51 ±0.1*	1.42 ±0.2	1.26 ±0.1*
CoP approach to $LoS_{anterior}$	4.83 ±1.3	5.66 ±0.8	5.89 ±1.5
CoP approach to $LoS_{posterior}$	2.94 ±0.8	3.55 ±1.2	3.72 ±2.3

* Statistically significant ($p<0.05$) differences between the controls and the PD fallers.
# Statistically significant ($p < 0.05$) differences between the PD fallers and the PD non-fallers.

4.5.2 Effect of muscle strength and balance ability on the dynamic stability control after simulated forward falls

A significant ($p<0.05$) relationship was found between recovery performance (b_x at release) and muscle strength (i.e. maximal isometric knee extension and plantarflexion moments, $R^2=0.33$ and $R^2=0.30$ respectively) (Fig. 4.2). Furthermore, we found a small ($R^2=0.19$) but significant relationship between the ability to approach to the anterior LoS and the recovery performance (Fig. 4.3). The ability to approach the CoP to the posterior LoS did not show any relationship to the recovery performance. Furthermore, the ability to approach the CoP to the anterior or posterior LoS did not relate to either the maximal knee extension ($R^2=0.012$ and $R^2=0.004$, respectively) or plantarflexion moments ($R^2=0.002$ and $R^2=0.002$, respectively).

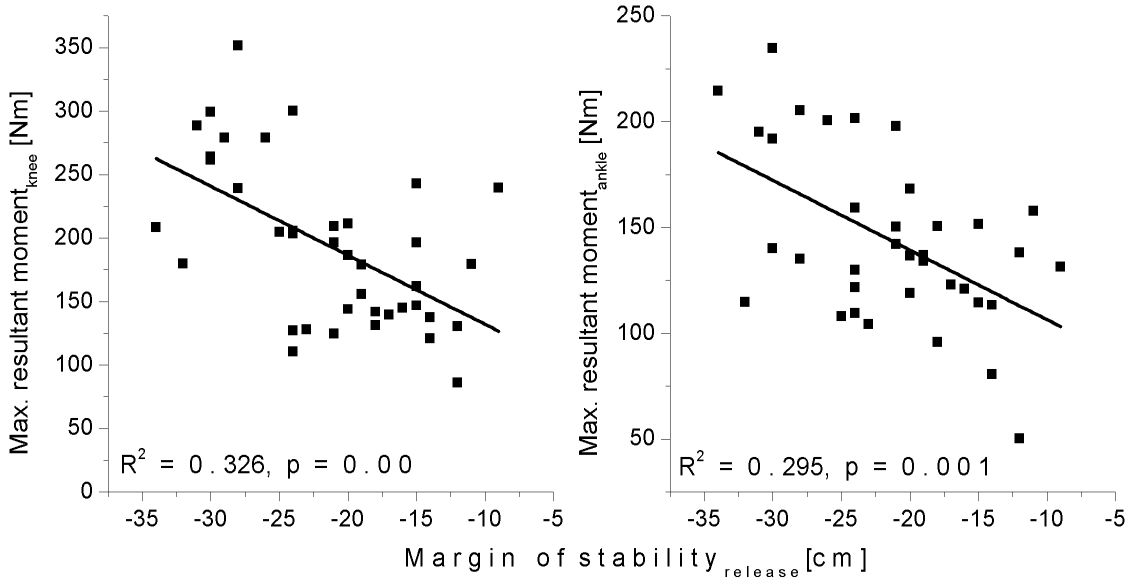

Fig. 4.2 Relationship between margin of stability at release and the maximal isometric knee extension (moment$_{knee}$) and ankle plantar flexion moments (moment$_{ankle}$) in the most inclined trial where the participants were able to recover with a single step during the forward fall task.

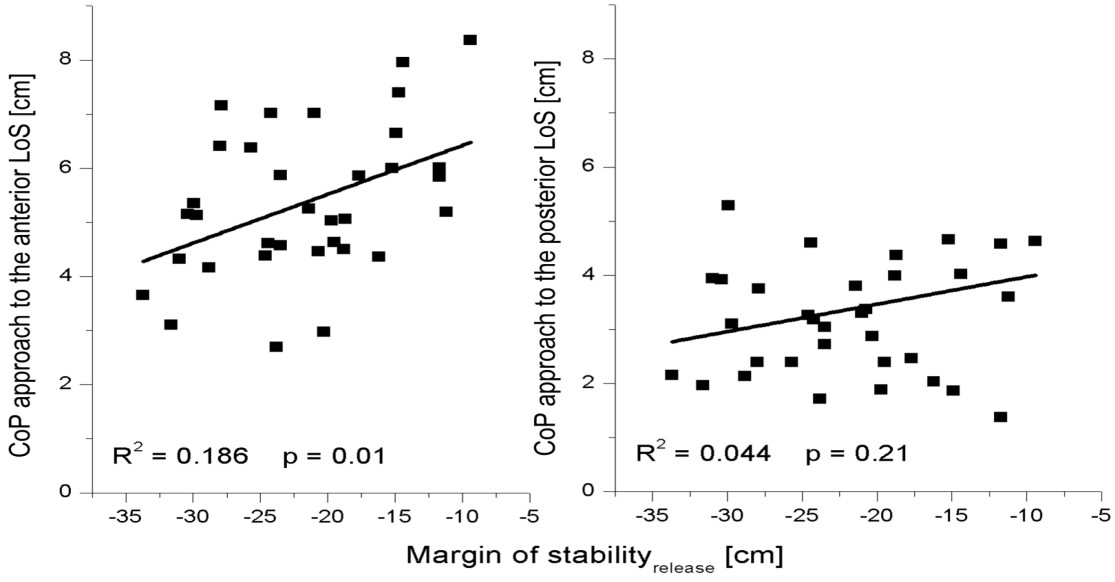

Fig. 4.3 Relationship between the maximal approach of the CoP to the anterior and the posterior limits of stability and margin of stability at release in the most inclined trial where the participants were able to recover with a single step during the forward fall task.

4.5.3 Classification of early-onset PD patients into fallers and non-fallers

A discriminant analysis demonstrated that, while recovery performance (i.e. b_x at release) could classify 60% of the PD fallers, the combination of the maximal isometric leg extensor`s moments together with the ability to approach the CoP to the anterior LoS could correctly classify up to 90% of the PD fallers in our study with a sensitivity level of 91% and a specificity level of 92%.

4.6 Discussion

The three investigated groups (i.e. healthy controls, PD non-fallers and PD fallers) demonstrated significant differences in recovery performance and muscle strength despite their equal level of sport activity, indicating that the exercise induced fitness of the patients was not the reason for the found deficits in PD fallers. Furthermore, the exclusion of elderly PD patients from the study enables us to assume that the deficits in muscle strength and stability performance were disease-related factors and not a consequence of the natural age-related degeneration. The young PD fallers demonstrated significant lower recovery performance after a sudden forward release. They were able to recover balance from a smaller lean angle compared to the matched healthy group. Muscle strength was also diminished in PD fallers and related to recovery performance (R^2=0.32). Furthermore, we found a small but significant relationship between b_x at release and the maximal approach of the CoP to the anterior LoS, indicating a moderate contribution of balance ability to recovery performance. Therefore our main hypothesis has been supported.

Recently Latt reported that muscle weakness in elderly PD patients was an important risk factor for falls (Latt et al., 2009a). To recover balance after a forward fall a rapid forward step initiated by joint torques of the lower extremities is needed (Walsh et al., 2011). Factors associated to muscle strength of the lower extremities, for example, rate of hip and ankle moment generation (Aragao et al., 2011; Arampatzis et al., 2011; Graham et al., 2013) and muscle power generation, are important factors that determine the stability performance during forward falls (Carty et al., 2012a; Carty et al., 2012b). It can be argued that decreased muscle strength in the lower extremities of the PD fallers is an important factor for their reduced stability performance after the investigated sudden forward release.

The most important deficit of PD fallers was an insufficient increase of the BS in relation to the extrapolated center of mass from release to TD and thus, an unstable position at TD. The lower BS when coupled with the absence of significant differences (p=0.62) in the duration from release until

TD between groups, indicates that the reason for the decreased stability performance in PD fallers was the velocity in which the boundary of the BS was shifted anteriorly after release. This means that the PD fallers executed the needed forward step slower than the other two groups and in this way they demonstrated deterioration in using the mechanism of increasing the BS. Using this mechanism rapidly after perturbations can improve the stability performance after forward falls (Arampatzis et al., 2011) as well as after unexpected gait perturbations (Bierbaum et al., 2013). Furthermore, it has been reported that the rate of hip and plantarflexion moment generation is associated to the ability to quickly use the above mechanism (Aragao et al., 2011; Arampatzis et al., 2011; Graham et al., 2013). The results show that young PD fallers were not able to generate adequate motor behavior for successful postural corrections after the simulated forward fall and that the muscle strength of the lower extremities is an important explanatory factor. This deficit in the use of the mechanisms responsible for maintaining dynamic stability after perturbations (i.e. sudden forward fall) may contribute to the higher frequency of falls in this group.

Similarly to several earlier studies (Nallegowda et al., 2004; Shen and Mak, 2012), we did not find an association between muscle strength and the ability to approach to the LoS, which demonstrates that both factors contribute independently (i.e. in a different manner) to the recovery performance. Burke reported that some aspects of balance, for example, the control of the amplitude of the CoP displacement are more related to sensorial perception (i.e. sensorial input to the central nervous system) and less to muscle strength (Burke et al., 2012). However, muscle strength and the ability to approach to the anterior LoS are two independent factors, which can correctly classify 90% of the young PD fallers, and therefore can be considered as a strong predictor of the falling risk in young PD patients. Both parameters can be easily measured and therefore represent a useful and applicable battery of tests for clinical contexts. The measurements of the muscle strength and the anterior approach to the LoS show a high reliability in PD patients (Intraclasscorelations: 0.97 and 0.81, respectively) supporting their applicability for fall prevention in PD patients (Paul et al., 2012b). Identifying patients with a high risk of falling already at a young age can enable the development of appropriate exercise therapy aiming to prevent and reduce the risk of falls. In this way, PD patients with an increased risk of falls may benefit from preventive therapy already at a young age and in the early stages of the disease. For example, strength training of the lower limbs and training exercising the mechanisms responsible for dynamic stability have been reported to increase stability performance in the elderly (Aragao et al., 2011; Arampatzis et al., 2011).

It is important to note that our findings on young PD patients may not be applicable to elderly PD patients because age related concurrent neuromuscular degeneration could affect the predictive strength of the investigated parameters (i.e. muscle strength and LoS). Furthermore, regarding the reported differences on disease evolution and effects of medication between early and late onset PD, the deficits found in young PD patients may not apply to older ones.

The retrospective assessment of the fall histories is a limiting factor in our study. Due to the poor accessibility of the PD patients, it was not possible to develop a systematic prospective analysis of their fall history. However, we used telephone interviews to examine the fall history between 6 and 18 months after the recording of the experimental data and they showed no significant differences in the falling rate of our participants before and after our experiments. This indicates that our PD faller group continued experiencing falls during the follow-up time, while the PD non-faller group remained stable, suggesting that our predicting factors would be valid also for prospective classification of PD fallers.

4.7 Conclusion

In conclusion, we found that young PD fallers present a reduced recovery performance after a sudden forward fall, which can be explained due to an insufficient use of the mechanism "increase of the BS". The ability to approach the CoP to the anterior LoS combined to muscle strength of the leg extensors can be used as a strong predictor of falling risk. This early identification of the PD patients with a high risk of falls at a young age may increase the effectiveness of exercise therapies aiming to prevent falls in early-onset PD patients. These therapies should focus on leg-extensors strengthening as well as on exercising the mechanisms responsible for dynamic stability control.

4.8 Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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5. Third study:

Reactive but not predictive locomotor adaptability is impaired in young Parkinson's disease patients

Authors:

María Moreno Catalá[1]

Dirk Woitalla[2]

Adamantios Arampatzis[1]

[1] Department of Training and Movement Sciences, Humboldt-Universität zu Berlin

[2] Department of Neurology, St. Joseph Hospital, Ruhr-Universtität Bochum

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5.1 Abstract

Background:
Gait and balance disorders are common in Parkinson`s disease (PD) and major contributors to the increased falling risk. Predictive and reactive adjustments can improve recovery performance after gait perturbations. However, these mechanisms have not been investigated in early-onset PD.

Objective:
We aimed to investigate the effect of gait perturbations on dynamic stability control as well as predictive and reactive adaptability to repeated gait perturbations in young PD patients.

Methods:
Fifteen healthy controls and twenty-five young patients (48±5 yrs.) walked on a walkway. By means of a covered exchangeable element the surface condition was altered to induce gait perturbations. The experimental protocol included a baseline on hard surface, an unexpected trial on soft surface and an adaptation phase with 5 soft trials to quantify the reactive adaptation. After the first and sixth soft trials, the surface was changed to hard, to examine after-effects and, thus, predictive motor control. Dynamic stability was assessed using the 'extrapolated center of mass' concept.

Results:
Patients` unperturbed walking was less stable than controls` and this persisted in the perturbed trials. Both groups presented after-effects directly after the first perturbation showing similar predictive responses. However, PD patients did not improve their reactive behavior after repeated perturbations while controls showed clear locomotor adaptation.

Conclusions:
More unstable gait patterns and a less effective reactive adaptation to perturbed walking seem to be a disease-related characteristic in young PD patients. These deficits were related to a reduced ability to increase the base of support, which is susceptible to training-induced improvements.

Key words: Parkinson`s Disease, young disease onset, dynamic stability, predictive and reactive gait adaptability.

5.2 Introduction

Postural instability is a major problem for Parkinson´s disease (PD). The falling rate of PD patients is five times higher than the one of age-matched controls, having a dramatic impact on patient`s mobility, independent living and quality of life (Bloem et al., 2001a; Bloem et al., 2004a). Nearly half of these falls occur during dynamic tasks, such as walking and turning (Ashburn et al., 2008). However, very little is known about the mechanisms underlying the gait disability in this population when walking in environments representative of real-world settings (Cole et al., 2011).

Parkinsonian gait is characterized by reduced walking velocity (Morris et al., 2001; Morris et al., 2005; Almeida et al., 2007), less foot clearance (Hausdorff, 2009; Horak and Mancini, 2013) and shorter stride length (Morris et al., 2001; Morris et al., 2005; Almeida et al., 2007). Especially the PD fallers show differences in walking velocity, stride timing variability and cadence compared to PD non-fallers (Latt et al., 2009a; Latt et al., 2009b). These deficits in the PD typical gait pattern may result in a reduction of the stability state during normal walking. However, gait analyses are usually made while walking on firm and predictable surfaces, which is not representative of the variable real-world circumstances. Unexpected gait perturbations are present in daily gait episodes and have been shown to decrease recovery performance leading to a higher occurrence of falls in older individuals (Thelen et al., 2000; Pijnappels et al., 2005b; Karamanidis and Arampatzis, 2007). In PD patients, given the above mentioned gait impairments, their risk of falling could be exacerbated under these conditions that challenge postural stability. For example, postural control deficits in elderly PD fallers may impair their capacity to attenuate surface-related perturbations produced by walking on compliant surfaces like a foam walkway (Cole et al., 2011).

From a biomechanical point of view, there are three mechanisms responsible for maintaining postural stability after perturbations: (a) increasing the base of support (BS), (b) counter-rotating segments around the center of mass (CM), and (c) applying an external force (not the ground reaction force) (Hof et al., 2005). Furthermore, recovery performance can be modified by predictive and reactive adaptive behavior. Reactive adjustments rely on the detection of unexpected perturbations and depend on sensory information received during the movement (Patla, 2003). On the other hand, predictive adjustments are based on the available knowledge about the intended movement (Patla, 2003; Bierbaum et al., 2013) and can improve dynamic stability by counteracting an expected perturbation during the ongoing movement, thus reducing its consequences (Marigold and Patla, 2002; Pai et al., 2003; Bierbaum et al., 2010).

PD patients show deficits in proprioception (Klockgether et al., 1995; Wright et al., 2010), which may result in a reduced adaptation potential to changing conditions (i.e. gait perturbations), which has been previously observed in elderly patients during obstacle crossing (Stegemoller et al., 2012).

Therefore, PD may impair reactive as well as predictive postural adjustments during gait, because sensory information is essential for the planning and execution of postural responses to maintain dynamic stability during perturbed walking (Patla, 2003). Predictive and reactive responses to perturbed gait termination have been reported to be normal in elderly PD patients; while their reactive adaptability after repeated perturbed trials has been shown to be reduced compared to controls (Oates et al., 2013). However in this study, PD patients walked significantly slower than controls (Oates et al., 2013). That caused an effect on the magnitude of the perturbation, which may result in not allowing an objective comparison of the adaptive responses between groups.

Age also plays a significant role in gait stability. New knowledge regarding elderly PD patients is not directly transferable to young patients, since it is well known that the ability to control stability deteriorates during natural aging process (Wojcik et al., 1999; Pijnappels et al., 2005a; Karamanidis and Arampatzis, 2007). There is a growing number of early-onset PD patients (under 51 years old) (Marder et al., 2010) suffering from gait and stability impairments (Bloem et al., 2001a; Voss et al., 2012). However, since the mean age of disease onset is around 65 years, very little is known about young PD patients` stability performance during perturbed walking. Identifying the deficits in dynamic stability control during disturbed walking, which relate to the underlying disease process in early-onset PD, without the influence of the natural age-related degeneration, would contribute to develop adequate training interventions aiming to reduce falls in young PD patients.

To date there is no information about young PD patients` locomotor adaptability in response to repeatedly perturbed walking. A deeper knowledge of the reactive and predictive locomotor adaptability to gait disturbances would help to understand the factors underlying gait disorders and increased falling risk in early PD. Therefore, this study aimed to investigate the effect of unexpected gait perturbations on dynamic stability control in young PD patients (in average ~ 48 yrs.) compared to age-matched healthy controls, and to examine the reactive and predictive adaptability following repeated exposure to the perturbation. We hypothesized less stable walking, greater consequences on stability after an unexpected perturbation and lower predictive as well as reactive locomotor adaptability in PD patients compared to healthy controls.

5.3 Methods

5.3.1 Participants

Fifteen healthy adults and twenty-five young patients with idiopathic PD participated in this study (Table 5.1). Patients were not included in the study if they had a history of any other neurological or an orthopedic disorder. Individuals were examined during the ON phase while taking a daily dose of dopaminergic medication ranged from 150 to 500 mg (levodopa) and 2 to 20 mg (dopamine-agonists). Controls were matched to the PD patients with respect to age, anthropometrics (weight and height) and sport activity level. Sport activity was quantified as hours per week of regular sport activity in the past year using a questionnaire. The work has been approved by the university ethic committee and the participants gave consent to the experimental procedure.

Tab. 5.1 Anthropometric data, age at disease-onset and stage in the Hoehn & Yahr Parkinson scale (H&Y) for the control and the PD group (means ± SD).

	Controls (n=15)	**PD patients** (n=25)
Age [yrs.]	47 ± 5	48 ± 5
Body mass [kg]	78.0 ± 14.6	77.6 ± 16.6
Body height [cm]	174 ± 12	172 ± 8
Body mass index [kg/m²]	25.3 ± 4	25.9 ± 4.5
Age at disease onset [yrs.]		42 ± 6
H&Y scale		2.0 ± 0.7

There were not statistically significant differences ($p>0.05$) in any of these parameters between groups.

5.3.2. Experimental protocol

The participants had to perform 11 walking trials on a walkway (12 x 0.6 x 0.2 m^3) which included an exchangeable element (75 x 60 x 20 cm^3) that was hidden with a cover sheet in order to be able to change the surface from hard to soft and vice versa without the knowledge of the participants (Fig. 5.1) (Bierbaum et al., 2010&2011). The soft element was made of foam with an upper surface

of relatively hard rubber (depth = 0.8cm). The deformation of the soft element during the walking trials was about 10 cm in depth featuring a nonlinear force-deformation characteristic. Although the participants were informed that something in the walkway might change, they were unaware of type and timing of the unexpected perturbation.

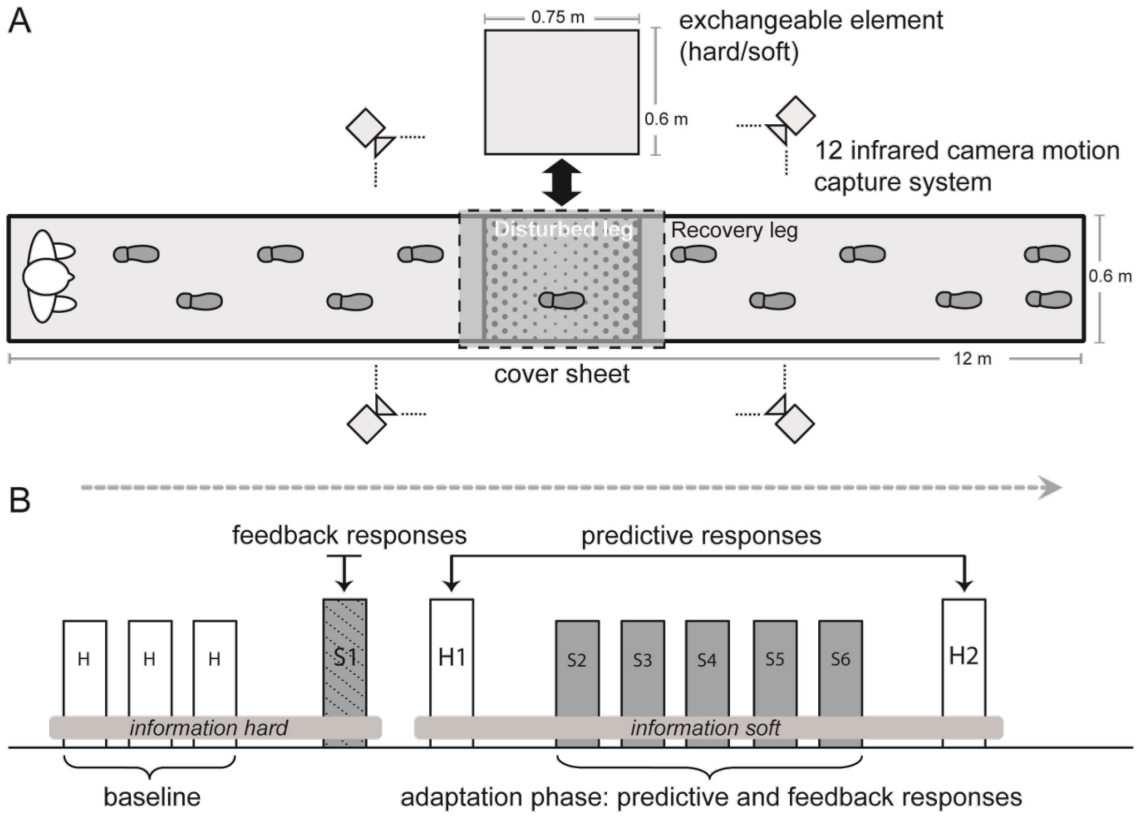

Fig. 5.1 Experimental setup and protocol**.**
(A) The walkway included one covered, exchangeable element, which allowed changing the surface condition from hard to soft and vice versa without the knowledge of the participants. (B) Three baseline trials on hard surface (H), was followed by one unexpected soft surface trial (S1). The next unannounced hard surface trial (H1) and the last hard surface trial (H2) after 5 soft trials were used to analyze predictive responses (after-effects). The soft surface trials (S2 to S6) documented the adaptation phase. The participants started the baseline trials with the information that they would have to expect a hard surface and continued after the first soft trial with the new information that the surface would stay soft.

The protocol (Fig. 5.1) started with three trials on hard surface (baseline) followed by an unexpected perturbation on soft surface to detect feedback responses after the perturbation (first step after the exchangeable element), since the participants could not anticipate the perturbation. In the following adaptation phase (i.e. 5 trials) on the soft surface the participants were told that the surface for all following trials would stay ''soft''. Two additional hard trials at the beginning (H1) and the end (H2) of the adaptation phase were performed to examine after-effects and thus predictive responses, since after-effects are a criterion for predictive motor adaptation (Martin et al., 1996; Fernandez-Ruiz and Diaz, 1999). The walking velocity of 1.3 m/s (which was a comfortable walking velocity for all patients) was controlled by a stick, which moved in front of

the participants along the walkway and by light barriers. The starting position of the participant was adjusted so that the participants would always step with their right leg on the exchangeable element.

5.3.3 Quantification of dynamic stability control

Three custom made contact mats (sampling rate 1080 Hz) were used to detect the touchdown and toe-off on the exchangeable walkway element and the steps before and after it. *Disturbed leg* refers to the leg that stepped on the exchangeable element and *recovery leg* to the leg that helped to regain balance after the perturbation (first step after the exchangeable element). Reactive and predictive responses were analyzed at touchdown of the recovery leg (TDrec) and disturbed leg (TDdist), respectively, to quantify the effectiveness of the mechanism "increasing the base of support" described by Hof (Hof et al., 2005).

Kinematic data were recorded with 12 Vicon cameras (120 Hz; Vicon, Oxford, UK). Twenty-one reflective markers (radius 14 mm) were used to track whole body kinematics (Bierbaum et al., 2013). The segmental masses and the location of the segments center of mass were calculated based on the data reported by Dempster (Dempster et al., 1959).

Dynamic stability control was quantified using the "extrapolated center of mass" concept formulated by Hof (Hof et al., 2005). The margin of stability (b_x), as a criterion for the state of stability of the human body, was calculated as:

$$b_x = U_{\max} - X_{CM} \qquad \text{(Eq. 5.1)}$$

where b_x indicates the margin of stability in the anterior-posterior direction, U_{max} is the anterior boundary of the BS and X_{CM} is the position of the extrapolated CM in the anterior-posterior direction defined as:

$$X_{CM} = P_{XCM} + \frac{V_{XCM}}{\sqrt{g/l}} \qquad \text{(Eq. 5.2)}$$

P_{XCM} is the horizontal (anterior-posterior) component of the projection of CM to the ground, V_{XCM} is the horizontal CM velocity and the term $\sqrt{g/l}$ represents the natural frequency of an inverted pendulum model of length l, where g is the acceleration of gravity and l is the distance between

CM and center of the ankle joint in the sagittal plane. Postural stability is maintained in circumstances where the position of the extrapolated CM is within the base of support (i.e. $b_x \geq 0$), while stability is lost in cases where the extrapolated CM passes the anterior boundary of the BS (i.e. $b_x < 0$) (Fig. 5.2).

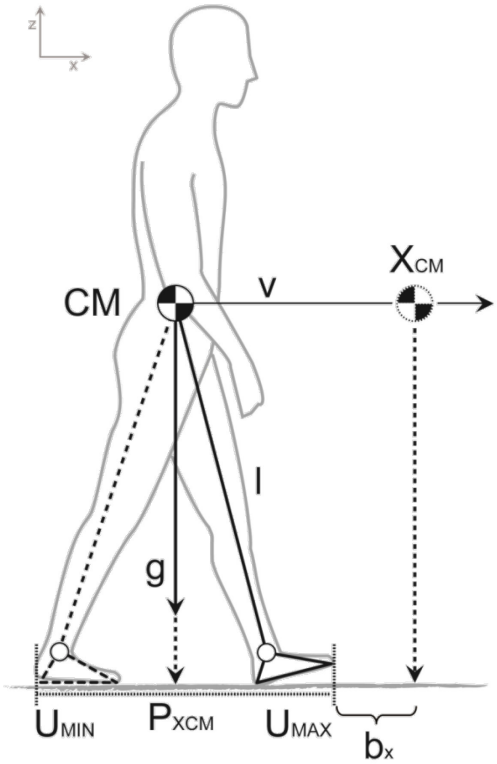

Fig. 5.2 Schematic diagram of the inverted pendulum model applied to walking**.** The human body is represented by a single mass *m* with the center of mass (CM) balancing on a pendulum of length *l* with respect to the acceleration of gravity *g*. P_{XCM} is the projected CM on the ground and *v* the CM velocity. U_{min} and U_{max} indicate the boundaries of the base of support (BS). The CM trajectory is extrapolated in the direction of its anterior–posterior velocity denoted as extrapolated center of mass (X_{CM}). The parameter 'margin of stability (bx)' as the anterior–posterior distance of the X_{CM} to the anterior boundary of the BS can be used as a criterion for the stability state of the human body.

5.3.4 Statistics

The mean values of three baseline trials on hard surface were averaged to establish the baseline level (B). The trials 4 (S5) and 5 (S6) of the adaptation phase were pooled together to quantify the adaptation to soft surface (S_{adap}) (Fig.5.1). In addition, the first trial on soft surface (S1, i.e. reactive response) and the two hard surface trials H1 and H2 (i.e. predictive response) were included in the analysis. An analysis of variance for repeated measures with trial (B, S1, S_{adap} and B, H1, H2) as inter-subject factor and group (PD patients and controls) as between-subject factor was used to examine the trial and group related differences in the dynamic stability parameters (margin of

stability, BS, position of the X_{CM}, P_{XCM} and V_{XCM}). When significant differences were detected, a post-hoc test (Bonferroni) was applied to determine where these differences occurred. A follow-up-test (t-test) was performed when significant trial x group interactions were detected. The level of significance was set to $\alpha = 0.05$. All results in the tables are presented as mean and standard deviation (SD) and in the figures as mean and standard error (SE).

5.4 Results

No significant differences were found between the PD and the control groups for the anthropometrics (Table 5.1).

5.4.1. Touchdown of the disturbed leg

During the baseline trials, the margin of stability was significantly lower ($p < 0.05$) in the PD group compared to controls (Fig. 5.3), reflecting more unstable gait patterns in unperturbed walking for the PD patients at the same walking velocity (1.3 m/s). Compared to the baseline, the margin of stability at TDdist increased significantly in both groups for the hard trials H1 and H2 (Fig. 5.3). This means that both groups showed after-effects very quickly (already after the first experience with the soft surface) and, thus, predictive adaptational responses following the first unexpected perturbation. Compared to baseline, the base of support did not change ($p>0.05$) in the H1 trial but increased significantly ($p<0.05$) in the H2 trial in both groups (Table 5.2). The anterior CM projection decreased significantly (i.e. with a greater posterior position relative to the anterior boundary of the BS) compared to baseline at touchdown in the H1 trial ($p<0.05$) but not in the H2 trial (Table 5.2).

5.4.2 Touchdown of the recovery leg

Compared to baseline, the margin of stability decreased after the first perturbation (S1) in both groups (Fig. 5.3), reflecting a more unstable position at TDrec as a consequence of the unexpected perturbation. We identified a trial x group interaction ($p=0.029$) showing that only the control group increased significantly their margin of stability during the adaptation phase, recovering baseline levels (Fig. 5.3). Compared to baseline, both groups showed a significant ($p<0.05$)

increase in the horizontal CM velocity at TDrec after the perturbation (Table 5.2). The BS at TDrec showed higher values ($p < 0.05$) for S1 and S_{adap} compared to baseline only in the control group (Table 5.2). Both groups showed in S1 a significant ($p<0.05$) increase of the projected and the extrapolated CM compared to baseline. The CM projection returned to baseline levels ($p>0.05$) at the end of the adaptation phase (Table 5.2). The CM velocity did not show any significant differences between groups (Table 5.2).

Tab. 5.2 Parameters of dynamic stability control at touchdown of the disturbed leg (TDdist) and touchdown of the recovery leg (TDrec).

(a)

	Touchdown of the disturbed leg (TDdist)					
	Controls (n=15)			**PD patients (n=25)**		
	Baseline	**H1**	**H2**	**Baseline**	**H1**	**H2**
BS [cm] ^{o}	96.2 ± 6.7	98.2 ± 7	98.4 ± 7.2	93.0 ± 4.6	92.6 ± 6.2	94.2 ± 5.6
V_{XCM} [m/s]	1.34 ± 0.0	1.36 ± 0.0	1.36 ± 0.1	1.38 ± 0.0	1.35 ± 0.1	1.39 ± 0.1
X_{CM} [cm]	84.7 ± 4.8	84.7 ± 4.9	85.0 ± 7.2	86.2 ± 3.8	83.5 ± 7.3	85.7 ± 6.5
P_{XCM} [cm] *	43.2 ± 2.6	42.7 ± 2.8	43.0 ± 3.5	43.8 ± 2.8	41.9 ± 3.9	42.9 ± 3.7

(b)

	Touchdown of the recovery leg (TDrec)					
	Controls (n=15)			**PD patients (n=25)**		
	Baseline	**S1**	**S_{adap}**	**Baseline**	**S1**	**S_{adap}**
BS [cm] $^{\# \Phi}$	93.0 ± 7.7	101.4 ± 9.7	97.8 ± 10.4	90.1 ± 4.1	92.8 ± 8.4	87.4 ± 10.3
V_{XCM} [m/s] $^{* o}$	1.31 ± 0.0	1.45 ± 0.0	1.38 ± 0.1	1.35 ± 0.0	1.46 ± 0.1	1.42 ± 0.1
X_{CM} [cm] $^{* o}$	79.9 ± 5.6	91.3 ± 6.2	84.4 ± 8.6	81.6 ± 3.2	88.2 ± 7.7	82.5 ± 8.1
P_{XCM} [cm] *	39.6 ± 3.2	47.2 ± 4.5	42.5 ± 4.8	40.1 ± 2.3	44.3 ± 5.1	40.2 ± 5.2

Mean ± SD of the base of support (BS), the horizontal velocity of the center of mass (V_{XCM}), the extrapolated center of mass (X_{CM}) and the horizontal component of the projected center of mass (CM) to the ground (P_{XCM}), for the control and PD groups at (a) baseline and at the following experimental hard trials (H1 and H2) and at (b) baseline, the first soft trial (S1) and the end of the adaptation phase (S_{adap}). BS, X_{CM} and P_{XCM} are calculated in reference to the anterior boundary of the posterior leg at touchdown of the recovery leg.
*: trial effect, the post hoc comparisons showed statistically significant differences between a) baseline and H1 or b) baseline and S1 ($p<0.05$).
^{o}: trial effect, the post hoc comparisons showed statistically significant differences between a) baseline and H2 or b) baseline and S_{adap} ($p<0.05$).
$^{\#}$: group effect, the post hoc comparisons showed statistically significant differences between controls and PD patients ($p<0.05$).
$^{\Phi}$: group x trial interaction showing statistically significant differences between baseline, S1 and S_{adap} only for the control group ($p<0.05$).

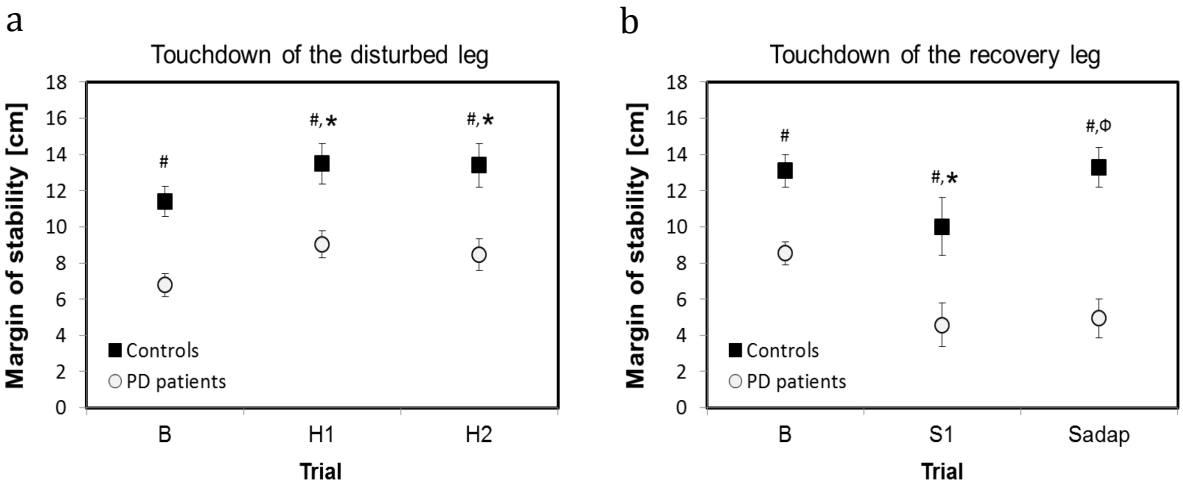

Fig. 5.3 Mean values and SE of the margin of stability (a) at touchdown of the disturbed leg in the baseline (B) and hard surface trials (H1 & H2) and (b) at touchdown of the recovery leg in the baseline (B) and soft surface trials (S1 & S_{adap}) for the control (n=15) and PD (n=25) groups.
*: statistically significant difference to the baseline for both groups ($p<0.05$).
#: statistically significant difference between groups ($p<0.05$).
Φ: significant trial x group interaction indicating an adaptation only for the control group ($p<0.05$).

5.5 Discussion

The current study examined the effect of environmental perturbations during gait with respect to dynamic stability control on young PD patients compared to age-matched controls. We found a lower stability state at the same walking velocity and lower adaptability during the repeated perturbations for the PD patients but similar predictive adaptational responses between controls and PD patients. Therefore, our hypotheses have been partly confirmed.

PD patients showed a more unstable locomotion during the unperturbed walking compared to controls. The significant decrease of ~40% in the stability state (originated by a tendency towards a smaller base of support and a more anterior position of the extrapolated CM) could increase the consequences of a gait perturbation during daily life, because both the type of the perturbation as well as the current state of the system influences the magnitude of the perturbation (Patla, 2003).

Controls as well as PD patients demonstrated similar after-effects in the first hard surface trial after the unexpected perturbation. They made use of the knowledge from the first perturbation and increased their stability (i.e. margin of stability) at touchdown of the disturbed leg in a predictive manner. However, the increase of margin of stability compared to baseline in H1 occurred rather

by a greater backward position of the CM (i.e. greater backward leaning of the body) and not by a clear increase of BS as in the H2 trial. This locomotor behavior indicates an incomplete predictive adaptation after the first experience with the soft surface for both groups. Nevertheless, the after-effects were similar to controls and indicate no PD-related impairments in the predictive locomotor adaptability in young patients. Predictive responses are important components for safety locomotion (Marigold and Patla, 2002; Pai et al., 2003; Patla, 2003) because they reduce the consequences of expected perturbations (Bierbaum et al., 2010; Bohm et al., 2012) and can decrease the risk of falls. Predictive control is associated with supraspinal structures (Bastian, 2006; Morton and Bastian, 2006; Jayaram et al., 2011) involving cognitive processes like attention and working memory (Strick et al., 2009), that may not be damaged in early stages of the disease in young patients. Thus, the increased risk of falls in young PD patients seems not to be associated to deficits in predictive motor control.

After the unexpected perturbation only controls significantly increased the BS compared to the baseline condition, which is considered to be one of the main mechanisms to restore balance after a perturbation (Bierbaum et al., 2010&2011). The young PD patients did not significantly increase the BS indicating less effective reactive responses to regain stability after the perturbation. Furthermore, the PD patients were not able to improve their stability state after the following perturbations during the adaptation phase. The main reason for this lack of improvement was an invariant BS during the adaptation phase. We found evidence of locomotor adaptation in the stability state in the control group that was related to an increase in the BS after the perturbation.

Reactive responses play a critical role for the maintenance of stability during locomotion since they adjust the system to the requirements of changing conditions (Patla, 2003) and, thus, improve recovery performance. PD-related impairments in the sensory-motor system (Wright et al., 2010; Hall et al., 2013) may be already present in early-onset patients which may affect the decreased reactive responses during perturbed walking, because they are highly depended on the sensory input, the central processing, selection and modulation of the respective motor response (Patla, 2003). It has been proposed that the primary reason for disturbed function in PD may lie in the changes in the gating, fast integration and processing of sensory inputs in the basal ganglia which then affect reactive motor outputs in response to perturbations (Abbruzzese and Berardelli, 2003; Konczak et al., 2009).

Reactive and predictive adjustments are separate components of postural control (Macpherson et al., 1989). It has been suggested that they may be modulated by distinct basal ganglia-cortical circuits (Hall et al., 2013). The ability to adapt predictively but not reactively to gait perturbations seems to be a PD-related characteristic in young patients. This is the first study showing unaltered predictive responses but deficient reactive adaptability after repetitive gait perturbations in early-onset Parkinson´s disease. Similar deficits in the stability performance (i.e. reactive responses) during gait have been reported in healthy elderly (Bierbaum et al., 2010&2011; Mersmann et al.,

2012) and have been suggested to be an important factor for the increased risk of falls in this population (Granacher et al., 2011; Bierbaum et al., 2013). In contrast to the investigated young PD patients, healthy old adults are able to adapt and improve their stability after repeated gait perturbations (Bhatt et al., 2006; Bierbaum et al., 2010&2011).

Recently, it has been reported that the ability to refine postural adaptations with task repetition is compromised by dopamine therapy (Hall et al., 2013). Dopamine saturation of the ventral striatum can decrease motor learning in PD (Gotham et al., 1988; Fern-Pollak et al., 2004). Furthermore, the above mentioned deterioration on spatial learning is higher in patients with less compared to those with greater motor impairments (Fern-Pollak et al., 2004; Hall et al., 2013). Therefore, one possible explanation for the lack of improvements in the stability state during the adaptation phase might be the deterioration of postural learning due to dopamine administration. The participants of the present study were very young featuring quite mild motor symptoms. Therefore, their striatum may have been excessively stimulated in the peak ON state (time point when the measurements were conducted) with a subsequent impairing effect on procedural learning.

The development of non-medication based therapies appears to be an important necessity to reduce the falling risk in young PD patients, especially when taking into account recent reports about the compromise of gait stability by levodopa in people with mild to moderate disease severity (Wright et al., 2010; Hall et al., 2013; Hung and Schwarzschild, 2013), including frequent levodopa-induced dystonia and dyskinesias reported in early-onset patients (Wickremaratchi et al., 2009a). This study provides valuable information about the important factors (i.e. increase of BS) which work deficiently but are susceptible to be trained in young PD patients in order to prevent falls during dynamic activities. Beneficial effects of exercise on movement and reactivity have been shown on PD patients as a result of an exercise induced increase in endogenous dopamine synthesis (Muller and Muhlack, 2010). Further, although to a smaller extend than healthy controls, elderly PD patients have shown to maintain the ability to adapt and store new walking patterns during split-belt treadmill walking (Roemmich et al., 2013). Practicing tasks including the mechanisms responsible for dynamic stability control may improve the selection process of these efferent motor commands, allowing young PD patients to apply these motor programs in an appropriate way during sudden perturbations or tripping. This would improve their ability to recover from perturbations, as it was previously shown in healthy elderly (Bierbaum et al., 2013). Nevertheless, our results indicate that young PD patients may need a more frequent exposure to gait perturbations than healthy controls, to induce adaptations in a feedback-controlled manner. This factor should be taken into consideration for the development of more effective training interventions aiming to improve dynamic stability and to reduce the risk of falling while walking. Since the capacity to adjust predictively remains unaltered, these training interventions should focus on the improvement of the reactive responses.

5.6 Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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6. Main findings and conclusions

The present thesis intended to provide deeper knowledge about the underlying factors responsible for the disease-specific increased risk of falling in early-onset Parkinson`s disease patients. Furthermore, it sought to develop a sensible instrument for the early identification of patients at a high risk of falling. The three experimental studies included in this thesis provide further evidence of the neuromuscular deficits responsible for postural instability and falls (i.e. fall risk factors) which are specific to the underlying process of the disease (independent of the ageing process) and susceptible to be improved by exercise in order to prevent falls during dynamic activities in young PD patients. They also provide a suitable instrument with a very high predictive power for early identification of young PD patients at a high risk of falls.

6.1 Neuromuscular deficits related to the risk of falling in young PD patients

In summary, young PD fallers differ from PD non-fallers in that they show central originated deficits in leg extensors` muscle strength (evidenced by increased antagonistic moments and activation deficit of the agonists during maximal voluntary contractions of the leg extensors) and impaired ability to apply the mechanism “increasing the base of support” in response to simulated forward falls, which results in decreased recovery performance, when comparing them to controls. However, young PD non-fallers exhibit similar muscle strength levels and recovery performance as healthy controls. Both muscle strength and the ability to approach the CoP to the anterior limit of stability were significantly associated with recovery performance. Furthermore, these two factors together were shown to correctly classify 90% of the young PD fallers. The current results showed that young PD patients exhibit less stable gait patterns (represented by a lower margin of stability during unperturbed walking at the same walking velocity) and less effective reactive responses to unexpected and repeated ground surface perturbations compared to healthy controls. On the other hand, patients show predictive adaptability to gait perturbations similar to controls.

The three investigated groups (i.e. healthy controls, PD non-fallers and PD fallers) demonstrated no significant differences in the number of hours of regular sport activity practice, indicating that the level (i.e. volume) of sport activity of the patients was not the reason for the deficits found in young PD fallers. Furthermore, the exclusion of elderly PD patients and other neurological diseases from the study enables us to assume that the deficits in muscle strength, stability performance and gait adaptability were disease-related factors and not a consequence of other diseases or the natural age-related degeneration.

The consequences of the results found in the young PD fallers may be decreased ability to select and generate adequate motor responses for successful postural corrections after the perturbation of their stability state, thus resulting in a higher risk and frequency of falls already at this young age and early stages of the disease. Compared to controls, PD fallers showed clear deficits in controlling stability by a protective stepping response reflecting their lesser ability to use mechanisms responsible for maintaining dynamic stability (i.e. increase of the base of support), and therefore, creating a less stable body position at touchdown (smaller margin of stability values) after forward falls. One could argue that the young PD fallers were not able to selectively activate only the most effective muscles for a given task (in this case leg extension and stepping response), suggesting impaired ability to optimize muscle synergy patterns. The lower voluntary activation in triceps surae and quadriceps femoris muscles indicates impairments in the ability to utilize the entire muscle potential of the most important muscles for locomotion. It is well known that a limited capacity to sufficiently generate high knee extension and ankle plantar flexion moments increases the risk of falls in healthy elderly (Pijnappels et al., 2008b). Furthermore model-based predictions show that the muscle strength of the legs affects minimal step length required for stability after a forward balance loss (weaker leg muscles require a greater minimal step length) (Wu et al., 2007). Likewise, the increase found in muscle co-activation of the antagonist muscles in young PD fallers generates certain postural stiffness, which may partially compensate for their weak postural muscle activation in response to small perturbations (Horak et al., 2005). However, in response to large perturbations, this stiffness reduces the visco-elastic properties of the body, which normally aid in absorbing perturbations (Bloem et al., 2001a; Allen, 2010), and impairs the generation of quick active muscle torques for adequate movements, such as stepping, arm movements, and trunk flexion (McIlroy and Maki, 1993; Horak et al., 1996; Dimitrova et al., 2004; Allen, 2010). Moreover, the above mentioned deficits in muscle strength potential were related to reduced ability to provide adequate and time effective motor responses as well as to deterioration in using the mechanism “increasing the base of support” in young PD patients. Prior studies have shown that these impairments in the neuromuscular system are limiting the stability performance (Moreland et al., 2004; Carty et al., 2012b) and that they play an important role in maintaining dynamic stability after perturbations (i.e. sudden forward falls and unexpected gait perturbations) in

healthy elderly (Arampatzis et al., 2011; Bierbaum et al., 2013). Therefore, it is likely that they might contribute to the higher frequency of falls in young PD patients.

On the other hand, PD patients (independent of their condition of being fallers or non-fallers) generally showed a more unstable gait pattern, less effective reactive responses and reduced locomotor adaptability to perturbations. All these locomotor characteristics can increase the risk of falling, especially after perturbations, and may contribute to the increased prevalence of falls reported in the PD patients' population compared with neurologically healthy controls (Nutt and Holford, 1996; Bloem et al., 2001a). These locomotor deficits have been previously related to an increased risk of falls in healthy elderly (Bierbaum et al., 2010&2011; Mersmann et al., 2012). A lower general dynamic stability state is prone to less successful recovery after gait perturbations in daily life since it may increase the consequences of the perturbation (because both the type of the perturbation as well as the current state of the system influences the magnitude of the perturbation (Patla, 2003)). Reduced reactive responses also impair the maintenance of stability during locomotion since they adjust the system to the requirements of changing conditions (Patla, 2003), thus, improving recovery performance when needed.

It has been suggested that the difficulty that PD subjects show in modifying their postural responses to biomechanical demands may be due to poor use of proprioceptive information (Zia et al., 2000) or to poorly developed internal representation of their body, which is necessary to customize motor programs (Horak et al., 2005). This suggestion is supported by other studies which have reported PD-related impairments in the sensory-motor system (Wright et al., 2010; Hall et al., 2013) as well as changes in the gating, fast integration and processing of sensory inputs in the basal ganglia, which may then affect reactive motor outputs in response to perturbations (Abbruzzese and Berardelli, 2003; Konczak et al., 2009). Our results regarding biomechanical stability parameters are in agreement with the presence of the above mentioned impairments already in early-onset patients.

The reason why PD fallers and non-fallers exhibit a similar level of impairment in response to gait perturbation may be related to the magnitude of the postural demand during the task. While in the simulated forward falls the magnitude of the postural demand (forward lean angle) was increased to the individual maximal level (until the participants were not able to recover it any more), during the gait perturbations the magnitude of the demand was kept constant and on a submaximal level, since all the participants could recover from the perturbation in all trials. Some other reports pointed out deficits in maximal effort responses in PD and their singular relation to postural instability. The PD-related impairments in subthalamic nucleus activity have been reported to influence maximal effort responses (e.g. fast hand grips or maximal voluntary muscle contractions) (Anzak et al., 2012). In the same way, the abnormal activity in this brain area has also been related to postural instability and falls since its stimulation with deep brain stimulation shows one of the biggest effects on postural instability and gait difficulty symptoms (Fasano et al., 2012). Yet maximal

effort responses are essential for the recovery performance during large perturbations, as has been previously shown in healthy elderly (Karamanidis et al., 2008; Pijnappels et al., 2008a), and their deterioration may be responsible for the increased prevalence of falls in the PD faller group.

The ability to adapt predictively but not reactively to gait perturbations seems to be a PD-related characteristic, which is independent of the condition of faller or non-faller in young patients. Reactive and predictive adjustments are separate components of postural control (Macpherson et al., 1989) and have been suggested to be modulated by distinct basal ganglia-cortical circuits (Hall et al., 2013). While feedback adjustments in locomotor output after disturbances are believed to be mainly controlled by lower neural centers (i.e. spinal cord or brain stem; (Morton and Bastian, 2006)), which are directly affected by Parkinson`s disease, predictive control is associated with supraspinal structures and the cerebellum in particular (Bastian, 2006; Morton and Bastian, 2006), which in turn seems to be involved in cognitive processes (e.g. attention, working memory) (Strick et al., 2009). These processes may not be essentially damaged in early stages of PD - especially in young patients - without signs of cognitive impairments, which could be responsible for deficits in predictive motor control during walking. This is the first study on young PD patients showing unaltered predictive responses but deficient reactive adaptability after repeated experience with perturbed walking.

Furthermore, the reported deficient reactive adaptability to repeated exposure to the gait perturbation could have been affected by dopamine administration. A recent study from Hall et al. (2013) suggests that the ability to refine postural adaptations with task repetition is compromised by dopamine therapy (Hall et al., 2013). These negative effects on learning in PD may result from dopamine saturation of the ventral striatum (Gotham et al., 1988; Swainson et al., 2000; Fern-Pollak et al., 2004), in which dopaminergic projections are still preserved in early PD (Kish et al., 1988; Broussolle et al., 1999; Hall et al., 2013). Furthermore, the above mentioned deterioration on spatial learning is higher in patients with lesser motor impairments than in those patients with greater ones (Fern-Pollak et al., 2004; Hall et al., 2013). Therefore, one possible explanation for the lack of improvements in the stability state during the adaptation phase might be the deterioration of postural learning due to dopamine administration. The participants of the present studies were very young with quite mild motor symptoms. Therefore, their striatum may have been excessively stimulated in the peak ON state (time point when the measurements were conducted) with a subsequent impairing effect on procedural learning.

While there are some similarities between elderly and young PD patients in the factors that our studies identified as responsible for increased postural instability, some of our findings contradict previous results found in elderly patients, giving evidence of the strong influence of aging on the analysis of the neuromuscular deficits responsible for the increased falling rate in PD. Recovery performance has not been investigated after simulated forward falls in elderly PD, however, studies analyzing stepping response after platform displacement on elderly PD patients have shown a

generally later, slower and smaller response, without distinction between fallers and non-fallers (Jacobs and Horak, 2006; King and Horak, 2008). In contrast, our results showed that this deficit seems not to be a general characteristic in early PD, but rather a deficit related to the condition of being a faller in young patients. In the same way, deficits in muscle strength in elderly PD patients have been consistently reported by the majority of studies using maximal isometric contractions (Pedersen and Oberg, 1997; Robichaud et al., 2004) and have also been related to the increased risk of falling in these patients (Allen et al., 2013; Paul et al., 2014); however, this muscle weakness has generally been shown to be present in elderly patients independent of their falling rate (Inkster et al., 2003; Paasuke et al., 2004; Falvo et al., 2008). On the contrary, the young PD non-fallers participating in our studies did not show any significant differences in muscle strength when compared to age-matched controls. Furthermore, elderly PD patients show impaired ability to control their antagonist muscles` activity (Dietz, 1993; Horak et al., 1996; Dimitrova et al., 2004), while only fallers exhibit these deficits at a young age, suggesting that the central deterioration of muscle strength is not present in young patients yet, but it is a specific deficit strongly associated to falls in early-onset PD. Balance ability represented by the LoS task, was not found to be impaired at all in our young patients, while other reports on elderly patients showed PD-related deficits in this task (Mancini et al., 2009; Menant et al., 2011; Shen and Mak, 2012). However, in both elderly and young patients, the ability to approach to the anterior LoS has been significantly related to stability performance during dynamic tasks, indicating a moderate yet significant correlation to the recovery performance after simulated forward falls in our young patients ($R^2 = 0.19$), to the turning test in elderly patients ($R^2 = 0.25$) (Cheng et al., 2014), and to falls (Paul et al., 2014). These results indicate that even if the balance ability does not show significant impairments at a young age, its deterioration may start lightly at early disease stages and advance further with increased disease severity affecting recovery performance. This suggestion is supported by the high classification power of young patients at a high risk of falling showed by this parameter in our discriminant analysis. Very little research has been conducted on PD patients` predictive and reactive adaptation capacity; however, some studies on elderly PD report similar results to those found in young PD on predictive adaptability (Bares et al., 2010; Oates et al., 2013; Roemmich et al., 2014). The ability to respond reactively to locomotor perturbations has been reported as normal in elderly PD (Dietz et al., 1995; Oates et al., 2013; Roemmich et al., 2013), however, these studies present methodological issues which do not allow for the comparison of the reactive responses of the patients with those of the healthy controls (i.e. different gait velocities or previous experience with the perturbation). Although smaller in extent than in healthy controls, the ability to adapt to new walking conditions and to store new walking patterns has been shown to be present in elderly PD (Oates et al., 2013; Roemmich et al., 2013). In contrast, the young PD patients that were examined in our study showed considerable reduced ability to adapt and improve their stability after repeated gait perturbations. Medication may be a reason why elderly PD patients show higher adaptation

capacity to repeated exposure to locomotor perturbations than young PD patients (Hall et al., 2013; Semrau et al., 2014), since medication-related dopamine saturation in the ventral striatum might be lower in elderly than in young patients.

6.2 Early classification of PD patients into fallers and non-fallers

Our results showed that the ability to approach the CoP to the anterior LoS combined with muscle strength of the leg extensors was a strong predictor of the falling risk in young PD patients, presenting a very high accuracy (90%), sensitivity (91%) and specificity (92%). This early differentiation of the PD patients at a high risk of falling already at a young age may allow primary prevention of falls and increase the effectiveness of exercise therapies aiming to prevent and reduce falls. Similar to earlier studies (Nallegowda et al., 2004; Shen and Mak, 2012), we did not find an association between muscle strength and the ability to approach to the LoS, which demonstrates that both factors contribute independently (i.e. in a different manner) to the recovery performance, confirming the strength of the predictive variables. Both parameters have shown a high reliability in PD patients (Paul et al., 2012b) and can be easily measured in ambulatory settings and therefore represent an excellent assessing method, useful for and applicable to clinical contexts.

These results reveal a very high prediction accuracy, considering that other fall predicting clinical tests in elderly PD have shown no more than 70 - 80 % accuracy (AUC 0.73 to 0.83) (Paul et al., 2013; Paul et al., 2014) and around 65% sensitivity (Bloem et al., 2001a). In addition, the strongest predicting factor for future falls has often been a history of previous falls (Ashburn et al., 2001b; Fasano et al., 2012; Paul et al., 2013), which does not allow primary prevention. Only few studies have analyzed potentially remediable physical fall risk factors without including prior falls in the predictive models (Latt et al., 2009a; Camicioli and Majumdar, 2010; Paul et al., 2014). Nevertheless, studies aiming to evaluate the accuracy, sensitivity and specificity of clinical tests for assessing the risk of falls in PD patients have been conducted with elderly or mixed participant groups (mean age >65) (Leddy et al., 2011a; Duncan and Earhart, 2012; Paul et al., 2012b). None of those studies have been conducted with an entirely early-onset PD population, or with an entirely young PD sample. This is the first study which has identified a specific and sensitive assessing method for the early discrimination of young PD patients at a high risk of falling.

6.3 Practical implications

With regard to practical implications and recommendations, this thesis provides relevant information for the development of alternative non-medication based therapies aiming to improve postural stability and reduce the risk and incidence of falls in young PD patients. It also provides an accurate assessment tool for the early identification of young PD patients at a high risk of falls.

Exercise interventions not only stimulate neuronal outgrowth, neurotrophic factor expression, synaptogenesis, and neurogenesis (Jones and Schallert, 1994; van Praag et al., 1999), but also induce a significant endogenous synthesis and release of dopamine in the stratium (Al-Jarrah et al., 2007; Muller and Muhlack, 2010), providing the possibility to reduce the intake of anti-parkinsonian medication in young patients. The possibility to develop and conduct an alternative therapy which is able to reduce the intake of exogenous dopamine has a high relevance in the treatment of young PD patients due to the fact that levodopa-resistance is often developed after a few years of treatment (Hung and Schwarzschild, 2013), in addition to the levodopa-induced frequent dyskinesias, dystonia and motor fluctuations typical in early-onset patients (Wickremaratchi et al., 2009a). Both the reduction of medication intake and the improvement of motor symptoms such as falls would not only increase patients` quality of life but also have a substantial economic impact on the health care system as stated by Johnson et al. (Johnson et al., 2013).

Regarding the underlying factors found to be responsible for deficits in gait and postural stability in young PD - and which are susceptible to improvement from physical training - specific exercise interventions should be developed and applied to early stage young PD patients. The presented results provide valuable information on the characteristics necessary in such a specific exercise intervention in order to be effective for young PD patients.

6.3.1 Training suggestions for the improvement of the neuromuscular deficits related to falls in young PD

Muscle strengthening and intense exercise are not interventions clinicians would consider when treating a patient with PD (Hirsch, 2009). Until recently, intense exercise was feared to worsen the symptoms of PD by perhaps increasing the underlying muscle tone or wearing off the little amount of dopamine still available, and so, for these patients, high intensity exercise was to be avoided (Hirsch, 2009). Indeed, high intensity, task complexity, saliency and novelty may be necessary to promote structural and metabolic plasticity in the brain and musculoskeletal systems of persons with PD (Hirsch et al., 2009). However, to date, most of the interventions utilize exercises previously prescribed for the frail elderly or older recurrent fallers, not really focusing on the specific neuromuscular deficits present in PD and especially in early-onset PD (Goodwin et al., 2011). These kinds of interventions are not only very ineffective for fall prevention in young PD; they are also very demotivating for young patients who usually are still completely physically active. Therefore, we recommend a higher training intensity to reduce the rate of falling in young PD patients.

Exercise interventions aiming to prevent falls in young PD patients should focus on high-intensity resistance training of the lower extremities and complex tasks exercising the mechanisms responsible for dynamic stability control putting special emphasis on the improvement of the reactive responses. These interventions should be planned on a long-term basis and a high volume of practice, since young patients have shown to have a diminished adaptation capacity compared to neurologically healthy individuals. They should also be conducted already at early disease stages and at a younger age, even if patients do not present noticeable motor impairments or their motor symptoms do not interfere with daily activities yet. Even at the time of diagnosis, body awareness and perception of time and distance may be distorted (Demirci et al., 1997; Riesen and Schnider, 2001), and patients rarely perceive their impairment or self-correct their smaller/slower everyday movement (Hirsch and Farley, 2009). Therefore, training interventions for fall prevention should be applied during the early post-diagnosis period, prior to loss of postural stability, in order to allow proactive treatment approaches.

Resistance training for individuals with PD has generally been shown to be effective in increasing strength, and in some cases, mobility. Until now this type of intervention has been conservatively approached (Falvo et al., 2008), with short duration and frequency and a small number of sets per muscle group (Toole et al., 2000; Scandalis et al., 2001). As young PD fallers have shown increased activation deficits and increased antagonists' co-activation, resistance training to promote neural adaptations is needed. As can be seen in literature on neurologically normal individuals, such modifications are indeed possible (Griffin and Cafarelli, 2005; Gabriel et al., 2006). Studies on healthy adults have found increments in the agonist activation (~ 26%) and reductions of the

antagonists co-activation (~17%) after 4 weeks (Tillin et al., 2011) and 6 months (Hakkinen et al., 1998) of relative high-intensity (75% RM) strength training and a combination of high-intensity (80% RM) and explosive strength training of the knee extensors, respectively. Increases in the maximal motor unit discharge rates of 15% (in young adults) and 49% (in older adults) have also been reported after 6 weeks of high-intensity (85-100% RM) dynamic and isometric knee extensors resistance training (Kamen and Knight, 2004). In the same way, maximal intensity (100% RM) strength training has been shown to decrease the degree of antagonistic co-activation by 20% in young healthy adults after only 8 weeks of training (Carolan and Cafarelli, 1992).

Research studies on strength training with elderly PD patients have shown an increased improvement in strength (7 – 57%) with increasing training intensity (60 – 80% 4RM) (Toole et al., 2000; Hirsch et al., 2003). These increases in muscle strength were associated with balance improvements (27%, measured by the EquiTest) (Toole et al., 2000; Hirsch et al., 2003). It has been also demonstrated that elderly PD individuals at early-stage progression can experience improvements similar to those of neurologically normal controls after resistance training, with concomitant functional improvements (14.4% increase in stride length) (Scandalis et al., 2001). Furthermore, resistance training combined with balance training has proven to result in greater improvements in balance in elderly PD patients (Hirsch et al., 2003), this having a bigger impact if the training intensity is suitably high (Falvo et al., 2008; Farley et al., 2008; Hirsch, 2009). In brief, high-intensity resistance training may be of therapeutic value to young PD patients to enhance neural drive to the agonist as well as decrease undesired co-activation of the antagonist muscles (Hakkinen et al., 1998; Tillin et al., 2011), both contributing to improve strength and movement control, and thus reduce falls.

Practicing tasks, including the mechanisms responsible for dynamic stability control, may improve the selection process of these efferent motor commands, allowing young PD patients to apply these motor programs appropriately and timely during sudden perturbations or tripping. Exercise that specifically involves movement of the center of mass, reactive responses like sudden stepping, gait under perturbed conditions, narrowing and increasing the base of support and minimizing upper limb support may produce the best results and improve their ability to recover from perturbations during daily dynamic activities, as has been previously shown in healthy elderly (Aragao et al., 2011; Arampatzis et al., 2011; Bierbaum et al., 2013). In fact, gait training (faster than preferred treadmill walking in different directions) and step training (consisting of suddenly turning the treadmill on and off while the subject stood in different directions: forwards, backwards, or sideways) have shown promising results on the reduction of falls in elderly PD patients (Protas et al., 2005), suggesting that, if applied with the right intensity, it could also have a positive effect on reactive responding and postural stability in young PD patients.

Considering all of the studies applying training interventions to reduce postural instability and falls in PD patients, only two controlled trials were successful in the reduction of the falling rate in PD

patients. When analyzing the strategies applied in these studies, we recognize the presence of muscle strength training, practice situations where gait is perturbed and reactive responses must be used, and repetitive use of the mechanisms responsible for dynamic stability control (i.e. stepping or increase of the base of support) (Protas et al., 2005; Ashburn et al., 2007). These strategies are suitable to improve the specific PD-related deficits found in our young patients, supporting our suggestion that more specific training interventions aiming to improve the deficits in postural stability caused by the underlying process of the disease would be more effective in preventing falls in PD.

6.3.2 Implementation of a sensitive predictive tool for the early classification of PD patients into fallers and non-fallers in clinical contexts

The high classification power of the variables found in our study (ability to approach de CoP to the LoS in the anterior direction and muscle strength of the lower limbs) allows not only for the early identification of young patients at a high risk of falls, but also the implementation of primary prevention strategies to avoid falls before injurious falls occur. This possibility can drastically reduce the fear of falling in PD patients, consequently positively affecting the level of daily physical activity (Bloem et al., 2004a) as well as quality of life (Franchignoni et al., 2005) in young patients.

An early identification of the patients with the need to reduce their risk of falls (i.e. their neuromuscular deficits related to falls) can indeed increase the effectiveness of the therapeutic intervention, since it would allow confronting the postural stability deficits at a relatively low degree of degeneration. Furthermore, the therapeutic benefit of an exercise intervention is much higher when patients increase or at least maintain their level of daily physical activity. This can be easily achieved if exercise interventions are applied at early degeneration stages i.e., at an early stage of the disease.

The simple applicability of this tool and its specificity makes it optimal for use in clinical contexts. Having the possibility to easily recognize the need for preventive exercise therapy to improve postural stability would increase the number of medical prescriptions to therapy and thus the rate of participation of the PD patients in such specific preventive exercise programs.

6.4 Limitations

The following limitations regarding the measurement and calculation of the variables used in our studies can be stated as follows:

- The retrospective assessment of the fall histories is a limiting factor in our study. Due to the poor accessibility of the PD patients, it was not possible to develop a systematic prospective analysis of their fall history. However, we used telephone interviews to examine the fall history between 6 and 18 months after the recording of the experimental data. Our limited recording did not show any significant differences in the falling rate of the interviewed participants before and after our experiments (non-fallers: falls before our study = 0 and after our study = 0; fallers: falls before our study = 2.5 and after our study = 1.7). This indicates that most of the PD fallers participating in our studies continued experiencing falls during the follow-up time, while the PD non-faller group remained stable, suggesting that our predicting factors could be valid also for prospective classification of PD fallers.
- Physical activity is an important co-variable when analyzing the ability to control dynamic stability. We tried to control this variable through use of a very detailed questionnaire and quantified this as hours per week of regular activity. However, since every kind of activity affects different aspects of the neuro-motor system and has a different and irregular intensity which cannot be quantified outside of controlled laboratory conditions, it is almost impossible to make an accurate quantification of the participants` daily physical activity or its quality.
- In the presented studies, dynamic stability was analyzed according to the "extrapolated center of mass" concept (Hof et al., 2005). This concept, based on the inverted pendulum model, allows the quantification of dynamic stability at discrete time points but simplifies some characteristics of the human system. The inverted pendulum model simplifies the human body and, therefore, the estimated stability state might feature discrepancies to the actual state of the complex human system. For example, accelerations of the leg or of the arms during the swing phase are not included in the model. Thus, greater excursions of the CM relative to the pendulum length may increase the above mentioned inaccuracies. However, these limitations should not affect our findings due to a similar systematic error for all investigated groups of participants and the previously reported and validated excellent conformity between the predictions of the model and human motor behavior in balance recovery (Arampatzis et al., 2008; Hof, 2008; Karamanidis et al., 2008).
- It is important to note that our findings on young PD patients may not be applicable to elderly PD patients. Regarding the reported differences on disease evolution and effects of

medication between early and late-onset PD, the deficits found in young PD patients may not apply to older ones. In the same way, the tool proposed in this study to classify young PD fallers may not be accurate for elderly patients.

6.5 New questions and future lines of research

This thesis aimed to gain insight into the underlying neuromuscular deficits related to the increased risk of falling in early-onset PD patients as well as the early identification of this risk at a young age. With regard to future studies, there are some open questions and proposed lines of future research.

Firstly, to completely understand the recovery mechanisms used by young PD patients and their adaptation capacity further research is needed. Regarding other PD specific destabilizing factors like the stopped posture, it would be very useful to analyze the adaptive movement responses of other body segments like arms and head or the trunk. Using the approach of Hof (2005), it is possible to analyze the percentual contribution of the mechanisms "moving the center of pressure" or "increasing the base of support" and "counter-rotating the segments around the center of mass" (Hof et al., 2005). This would provide interesting information regarding the behavior of young PD patients during recovery tasks or perturbed walking as well as their adaptational strategies to repeated perturbations. In this way, deeper knowledge of the origin and meaning of the muscle synergies related to recovery performance would also contribute to a better understanding of the motor impairments in PD patients and, therefore help design more effective rehabilitative strategies. A possible way to study the involvement of the CNS in the generation of the muscular synergies is to observe brain activity (non-invasively recorded with an EEG system) and its correlation with muscle activity (with Electromyography). Moreover, techniques of source localization could be used to localize brain activity providing more insight into the neurophysiological origin and meaning of the muscle synergies.

Secondly, the most logical following step in the direction of fall prevention would be to develop a specific training intervention suitable to improve the neuromuscular deficits found in our young PD patients. Using the reported tool to identify young PD patients at a high risk of falls at an early stage would allow for the differentiation of those patients from the general community of PD patients and a specific training therapy could be properly applied in a timely fashion to enable primary fall prevention before injurious falls occur and the fear of falling increases. This early application of a specific fall prevention therapy would increase its efficacy and benefits in young

PD patients. The identified factors related to falls are susceptible to improvement by training, as has been previously reported in healthy elderly. However, these factors have been seldom trained in elderly PD patients and far less in young patients. It remains unclear to which extent these deficits could be improved by training and how it would affect young patients` postural stability and rate of falls. Specific training interventions should be evaluated, including specific biomechanical measures (kinematic, kinetic and electromyographic (i.e. muscle synergies concept) measures during reactive and anticipatory postural tasks) characteristic of the deficits related to young patients` postural instability.

It would be also very useful to analyze the effect of these specific training interventions on neural adaptation and disease progression in young patients. The assessment of the effect of specific exercise on fall prevention as well as on other motor symptoms, rather than postural stability, would contribute to the better adjustment and even reduction of antiparkinsonian medication, thus delaying the appearance of levodopa-related disabling side effects often present in early-onset PD.

In addition, deeper knowledge of the underlying processes triggered by these interventions in the brain would provide more accurate insight of the effectiveness of the training strategies on the delay of disease progression, and especially on fall prevention. Although this thesis does not deal with biomarkers, there is strong evidence that more research in this field would be very helpful for this purpose. Biomarkers offer the potential to provide a window into disease mechanism and the possibility to monitor disease progression as well as the effectiveness of therapeutical interventions (Baba and Takeda, 2012). In particular, biomarkers enable investigation of the premotor period of PD before typical symptoms are manifest, but once degeneration has already begun (Marek et al., 2009; Baba and Takeda, 2012). The investigation of biomarkers would allow for the identification and understanding of the relationship between small neuromuscular improvements and changes in neurophysiological disease progression already in early disease stages. This accurate monitoring of PD progression throughout its course would dramatically accelerate research into both PD cause and treatment (Marek et al., 2009). Positron emission tomography (PET) is a useful technique for the consecutive investigation of the relationship between changes in neurotransmission biomarkers and behavioral signs in animal models of Parkinson's disease (PD). PET with Dopamin transporter marker could be a suitable biomarker for early diagnosis at the presymptomatic stage of PD (Nagai et al., 2007) and for the identification and monitoring of impairments in high-risk patients.

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Appendix

Rating scales in Parkinson's disease

Hoehn and Yahr staging	
Stage 0	No signs of disease
Stage 1	Unilateral involvement only usually with minimal or no functional disability
Stage 2	Bilateral or midline involvement without impairment of balance
Stage 3	Bilateral disease: mild to moderate bilateral disability with impaired postural reflexes; physically independent
Stage 4	Severe disabling disease; still able to walk or stand unassisted
Stage 5	Wheelchair bound or bedridden unless aided

Modified Hoehn and Yahr staging	
Stage 0	No signs of disease
Stage 1	Unilateral involvement only
Stage 1.5	Unilateral plus axial involvement
Stage 2	Bilateral involvement without impairment of balance
Stage 2.5	Mild bilateral disease with recovery on pull test
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severe disability; still able to walk or stand unassisted
Stage 5	Wheelchair bound or bedridden unless aided

Unified Parkinson's disease Rating Scale (UPDRS)

I <u>Mentation, Behaviour & Mood</u>

1 Intellectual impairment
- 0 = none
- 1 = mild, consistent forgetfulness
- 2 = moderate, difficulty with complex problems
- 3 = severe, disorientation for time & place
- 4 = severe, help with personal care. Cannot be left alone

2 Thought disorder
- 0 = none
- 1 = vivid dreaming
- 2 = "benign" hallucination with insight retained
- 3 = hallucination or delusions without insight
- 4 = persistent hallucination, delusions, or florid psychosis

3 Depression
- 0 = not present
- 1 = periods of sadness or guilt > normal, never sustained for days/weeks
- 2 = sustained depression for >1 week
- 3 = vegetative symptoms (insomnia, anorexia, weight loss)
- 4 = vegetative symptoms and suicidal thoughts

4 Motivation/Initiative
- 0 = normal
- 1 = less assertive than usual, more passive
- 2 = loss of initiative/disinterest in elective activities
- 3 = loss of initiative/disinterest in routine activities
- 4 = withdrawn, complete loss of motivation

II <u>Activities of Daily Living</u>

5 Speech
- 0 = Normal
- 1 = Mildly affected
- 2 = Moderately affected. Sometimes asked to repeat statements
- 3 = Severely affected. Frequently asked to repeat statements
- 4 = Unintelligible most of the time

6 Salivation
- 0 = Normal
- 1 = Slight saliva excess. Some night-time drooling
- 2 = Moderately excessive saliva; minimal drooling
- 3 = Marked excess saliva with some drooling
- 4 = Marked drooling, requires constant tissue/handkerchief

7 Swallowing
- 0 = Normal
- 1 = Rare choking
- 2 = Occasional choking
- 3 = Requires soft food
- 4 =Requires nasogastric tube or gastrostomy feeding

8 Handwriting
- 0 = Normal
- 1 = Slightly slow or small
- 2 = Moderately slow/small; all words are legible
- 3 = Severely affected; not all words are legible
- 4 = The majority of words are not legible

9 Cutting food and handling utensils
- 0 = Normal
- 1 = Somewhat slow and clumsy, but no help needed
- 2 = Can cut most foods slowly; some help needed
- 3 = Food must be cut by someone, but can still feed slowly
- 4 = Needs to be fed

10 Dressing
- 0 = Normal
- 1 = Somewhat slow, but no help needed
- 2 = Occasional assistance with buttons, arms in sleeves
- 3 = Considerable help, can do some things alone
- 4 = Helpless

11 Hygiene
- 0 = Normal
- 1 = Somewhat slow, no help needed
- 2 = Help to shower/bathe
- 3 = Assistance for washing hair, brushing teeth & hair
- 4 =Foley catheter or pads

12 Turning in bed & adjusting bed clothes
- 0 = Normal
- 1 = Somewhat slow & clumsy, no help needed
- 2 = Turns alone or adjusts sheets, but with difficulty
- 3 = Can initiate, but not turn or adjust sheets alone
- 4 = Helpless

13 Falling
- 0 = None
- 1 = Rare falling
- 2 = Occasionally falls, < 1 per day
- 3 = Falls on average once per day
- 4 = Falls > once per day

14 Freezing when walking
- 0 = None
- 1 = Rare freezing; may have start-hesitation
- 2 = Occasional freezing when walking
- 3 = Frequent freezing. Occasional falls resulting
- 4 = Frequent falls from freezing

15 Walking
- 0 = Normal
- 1 = Mild difficulty. May not swing arm or may drag leg
- 2 = Moderate difficulty, but requires no assistance
- 3 = Severe disturbance, requires assistance
- 4 = Cannot walk, even with assistance

16 Tremor *(Symptomatic complaint in any body part)*
- 0 = Absent
- 1 = Slight & infrequently present
- 2 = Moderate; bothersome to patient
- 3 = Severe; interferes with many activities
- 4= Cannot walk, even with assistance

17 Sensory complaints relating to parkinsonism
- 0 = None
- 1 = Occasional numbness, tingling or aching
- 2 = Frequent numbness, tingling or aching
- 3 = Frequent painful sensations
- 4 = Excruciating pain

III <u>Motor examination</u>

18 Speech
- 0 = Normal
- 1 = Slight loss of expression, diction or volume
- 2 = Monotone, slurred but understandable
- 3 = Marked impairment, difficult to understand
- 4 = Unintelligible

19 Facial expression
- 0 = Normal
- 1 = Minimal hypomimia, could be 'poker face'
- 2 = Definite diminution of expression
- 3 = Moderate hypomimia; lips parted some of the time
- 4 = Masked or fixed facies; lips parted ¼ inch or more

20 Tremor at rest - Right upper limb
0 = Absent
1 = Slight, infrequently present
2 = Mild amplitude & persistent or moderate & intermittent
3 = Moderate amplitude, present most of the time
4 = Marked amplitude, present most of the time

Tremor at rest - Left upper limb
0 = Absent
1 = Slight, infrequently present
2 = Mild amplitude & persistent or moderate & intermittent
3 = Moderate amplitude, present most of the time
4 = Marked amplitude, present most of the time

Tremor at rest - Right lower limb
0 = Absent
1 = Slight, infrequently present
2 = Mild amplitude & persistent or moderate & intermittent
3 = Moderate amplitude, present most of the time
4 = Marked amplitude, present most of the time

Tremor at rest – Left lower limb
0 = Absent
1 = Slight, infrequently present
2 = Mild amplitude & persistent or moderate & intermittent
3 = Moderate amplitude, present most of the time
4 = Marked amplitude, present most of the time

21 Action or posture tremor of hands – Right hand
0 = Absent
1 = Slight, present with action
2 = Moderate in amplitude, present with action
3 = Moderate in amplitude, with posture holding & action
4 = Marked in amplitude; interferes with feeding

Action or posture tremor of hands – Left hand
0 = Absent
1 = Slight, present with action
2 = Moderate in amplitude, present with action
3 = Moderate in amplitude, with posture holding & action
4 = Marked in amplitude; interferes withfeeding

22 Rigidity *(judged on passive movement of major joints with patient relaxed in the sitting position)*

Rigidity - neck
0 = Absent
1 = Slight, detectable only with mirror movements
2 = Mild to moderate
3 = Marked, but full range of movement easily achieved
4 = Severe, range of movement achieved with difficulty

Rigidity – Right upper limb
0 = Absent
1 = Slight, detectable only with mirror movements
2 = Mild to moderate
3 = Marked, but full range of movement easily achieved
4 = Severe, range of movement achieved with difficulty

Rigidity – left upper limb
0 = Absent
1 = Slight, detectable only with mirror movements
2 = Mild to moderate
3 = Marked, but full range of movement easily achieved
4 = Severe, range of movement achieved with difficulty

Rigidity – right lower limb
0 = Absent
1 = Slight, detectable only with mirror movements
2 = Mild to moderate
3 = Marked, but full range of movement easily achieved
4 = Severe, range of movement achieved with difficulty

Rigidity – left lower limb
0 = Absent
1 = Slight, detectable only with mirror movements
2 = Mild to moderate
3 = Marked, but full range of movement easily achieved
4 = Severe, range of movement achieved with difficulty

23 Finger taps (*patient taps thumb with index finger in rapid succession with widest amplitude possible)*

Finger taps - Right hand
0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

Finger taps - Left hand
0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

24 Hand movements *(Patient opens & closes hands in rapid succession with widest amplitude possible)*

Hand movements – Right hand
0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

Hand movements – Left hand
0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

25 Rapidly alternating hand movements *(pronation-supination movements with as large an amplitude as possible)*

Rapidly alternating hand movements – Right hand
0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

Rapidly alternating hand movements – Left hand
0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

26 Leg agility *(rapid heel tapping. Amplitude ≥ 3 inches)*

Leg agility – Right heel

0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

Leg agility – Left heel

0 = Normal
1 = Mild slowing and/or reduction in amplitude
2 = Definite & early fatiguing; occasional arrests
3 = Frequent hesitation in initiation or arrests in movement
4 = Can barely perform the task

27 Arising from a chair *(patient's arms across chest)*

0 = Normal
1 = Slow; or may need more than 1 attempt
2 = Pushes self up from arms of seat
3 = May fall back or try more than once to get up
4 =Unable to arise without help

28 Posture

0 = Normal erect
1 = Slightly stooped; could be normal for older person
2 = Moderately stooped; can be slightly leaning to 1 side
3 = Severely stooped with kyphosis; can be moderately leaning to one side
4 = Marked flexion with extreme abnormality of posture

29 Gait

0 = Normal
1 = Walks slowly, short steps but no festination
2 = Walks with difficulty but without assistance; festination, short steps or propulsion
3 = Severely disturbed gait; requires assistance
4 =Cannot walk even with assistance

30 Postural stability (pull test, may have practice runs)

0 = Normal
1 = Retropulsion, but recovers unaided
2 = Absence of posture response, would fall if not caught
3 = Very unstable, spontaneous loss of balance
4 = Unable to stand without assistance

31 Body bradykinesia & hypokinesia (slowness, hesitancy, decreased arm swing, small amplitude & poverty of movement)

0 = None
1 = Minimal slowness, deliberate character, possibly reduced amplitude
2 = Mild slowness, poverty or small amplitude of movement
3 = Moderate slowness, poverty or small amplitude of movement
4 = Marked slowness, poverty or small amplitude of movement

IV Complications of therapy *(in the past week)*

A DYSKINESIAS

32 Duration: What proportions of the waking day are dyskinesias present?

0 = None
1 = 1 – 25% of the day
2 = 26 – 50% of the day
3 = 51 – 75% of the day
4 =76 – 100% of the day

33 Disability: How disabling are the dyskinesias?

0 = Not disabling
1 = Mildly disabling
2 = Moderately disabling
3 = Severely disabling
4 =Completely disabled

34 Painful dyskinesias: How painful are the dyskinesias?

0 = None
1 = Slight
2 = Moderate
3 = Severe
4 =Marked

35 Presence of early morning dystonias

0 = No 1 = Yes

B CLINICAL FLUCTUATIONS

36 Are any 'off' periods predictable as to timing after medication dosing?

0 = No 1 = Yes

37 Are any 'off' periods unpredictable as to timing after medication dosing?

0 = No 1 = Yes

38 Do any of the 'off' periods come on suddenly (seconds)?

0 = No 1 = Yes

39 What percentage of the waking day is the patient 'off' on average?

0 = None
1 = 1 – 25% of the day
2 = 26 – 50% of the day
3 = 51 – 75% of the day
4 =76 – 100% of the day

C OTHER COMPLICATIONS

40 Does the patient have anorexia nauseas or vomiting?

0 = No 1 = Yes

41 Does the patient have any sleep disturbance?

0 = No 1 = Yes

42 Does the patient have symptomatic orthostasis?

0 = No 1 = Yes

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Eidesstattliche Erklärung/Statutory Declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources / resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Ich erkläre, dass ich die vorliegende Dissertation selbständig und nur unter Verwendung der angegebenen Hilfsmittel angefertigt habe. Alle Zitate sowie sinngemäße wörtliche Wiedergaben, die anderen Werken entnommen wurden, sind unter Angabe der Quelle kenntlich gemacht. Die Abbildungen, Diagramme und Tabellen sind von mir erstellt, sofern diese nicht als Entlehnung gekennzeichnet sind. Weder diese noch eine andere Arbeit wurde von mir an einer anderen Universität oder Hochschule zum Zwecke der Einleitung eines Promotionsverfahrens vorgelegt.

Berlin, 17.06.2015

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María Moreno Catalá